



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>C07H 21/04, C07K 14/705, C12N 15/09, 15/63, C12Q 1/68</b>		A1	(11) International Publication Number: <b>WO 99/20644</b> (43) International Publication Date: <b>29 April 1999 (29.04.99)</b>
(21) International Application Number: <b>PCT/US98/22034</b> (22) International Filing Date: <b>16 October 1998 (16.10.98)</b>		(74) Agent: SPRUNGER, Suzanne, A.; American Home Products Corporation, Patent & Trademark Dept. – 2B, One Campus Drive, Parsippany, NJ 07054 (US).	
(30) Priority Data: <b>08/955,557 18 October 1997 (18.10.97) US</b>		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 Cambridge Park Drive, Cambridge, MA 02140 (US).		Published <i>With international search report.</i>	
(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 113 Ann Lee Road, Harvard, MA 01451 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). MERRBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). EVANS, Cheryl; 111 Locust Street #41, Woburn, MA 01801 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). BOWMAN, Michael, R.; 50 Aldrich Road, Canton, MA 02021 (US). AGOSTINO, Michael, J.; 26 Wolcott Avenue, Andover, MA 01810 (US).		(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM	
(57) Abstract  Novel polynucleotides and the proteins encoded thereby are disclosed.			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

## SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of the following applications: Ser. No. 08/677,231, filed July 9, 1996; Ser. No. 08/701,819, filed August 23, 1996; Ser. No. 10 08/721,488, filed September 27, 1996; and Ser. No. 08/739,066, filed October 28, 1996.

15

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these 15 polynucleotides and proteins.

20

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the 20 past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence 25 cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. 30 It is to these proteins and the polynucleotides encoding them that the present invention is directed.

30

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising

an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 179 to nucleotide 742;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568;
- 10 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;
- 15 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;
- 20 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of 25 (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1

from nucleotide 179 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568; the nucleotide sequence of the full-length protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
- (b) the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129;
- (c) fragments of the amino acid sequence of SEQ ID NO:2; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:3 from nucleotide 218 to nucleotide 1126;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:3 from nucleotide 1 to nucleotide 553;

5 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;

10 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101;

15 (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

20 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

25 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 218 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553; the nucleotide sequence of the full-length protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC222\_1 deposited

under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

5 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

10 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:4;
- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131;
- 15 (c) fragments of the amino acid sequence of SEQ ID NO:4; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

20 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994;
- 25 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101;

5

- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

15

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994; the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994; the nucleotide sequence of the full-length protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20.

20

25

30

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising

a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:6;
- (b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20;
- (c) fragments of the amino acid sequence of SEQ ID NO:6; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- 5 (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

10 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204; the nucleotide sequence of the full-length protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101.

15 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

20 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:8;
- (b) fragments of the amino acid sequence of SEQ ID NO:8; and
- (c) the amino acid sequence encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;

25 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8.

30 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:9 from nucleotide 1 to nucleotide 323;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101;

5 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101;

10 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101;

15 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

20 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID

NO:9 from nucleotide 60 to nucleotide 230; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 323; the nucleotide sequence of the full-length protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) fragments of the amino acid sequence of SEQ ID NO:10; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

AK684\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;

- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;
- 5 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- 10 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186; the nucleotide sequence of the full-length protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101.

20 In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

25 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:12;
- (b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to
- 30 amino acid 125;
- (c) fragments of the amino acid sequence of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

5 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890;

15 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180;

20 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180;

25 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

30 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

5 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708; the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890; the nucleotide sequence of the full-length protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180; or the nucleotide sequence of the mature protein coding sequence of clone 10 AX56\_28 deposited under accession number ATCC 98180. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180.

15 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

20 (a) the amino acid sequence of SEQ ID NO:14;

(b) fragments of the amino acid sequence of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14.

25 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID 30 NO:15 from nucleotide 51 to nucleotide 1319;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:15 from nucleotide 126 to nucleotide 1319;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:15 from nucleotide 409 to nucleotide 495;

(e) a polynucleotide comprising the nucleotide sequence of the full-

5 length protein coding sequence of clone AX92\_3 deposited under accession  
number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the  
cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101;

10 (g) a polynucleotide comprising the nucleotide sequence of the  
mature protein coding sequence of clone AX92\_3 deposited under accession  
number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the  
cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101;

15 (i) a polynucleotide encoding a protein comprising the amino acid  
sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the  
amino acid sequence of SEQ ID NO:16 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of  
20 (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the  
protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent  
conditions to any one of the polynucleotides specified in (a)-(j).

25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID  
NO:15 from nucleotide 51 to nucleotide 1319; the nucleotide sequence of SEQ ID  
NO:15 from nucleotide 126 to nucleotide 1319; the nucleotide sequence of SEQ ID  
NO:15 from nucleotide 409 to nucleotide 495; the nucleotide sequence of the full-length  
protein coding sequence of clone AX92\_3 deposited under accession number ATCC  
98101; or the nucleotide sequence of the mature protein coding sequence of clone  
30 AX92\_3 deposited under accession number ATCC 98101. In other preferred  
embodiments, the polynucleotide encodes the full-length or mature protein encoded by

the cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

5 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) fragments of the amino acid sequence of SEQ ID NO:16; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

10 AX92\_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid

sequence of SEQ ID NO:19;

- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

10 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350; the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350; the nucleotide sequence of the full-length protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone 15 BF245\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18, SEQ ID NO:17 or SEQ ID NO:20.

20 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:19;
- (b) fragments of the amino acid sequence of SEQ ID NO:19; and
- (c) the amino acid sequence encoded by the cDNA insert of clone 25 BF245\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:19.

30 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774;

5 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101;

10 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101;

15 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

20 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

25 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774; the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477; the nucleotide sequence of the full-length protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101. In other preferred

embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

5 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the 10 group consisting of:

- (a) the amino acid sequence of SEQ ID NO:22;
- (b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121;
- (c) fragments of the amino acid sequence of SEQ ID NO:22; and
- (d) the amino acid sequence encoded by the cDNA insert of clone 15 BG33\_7 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22 or the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

20 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BM46\_10 deposited under accession 25 number ATCC 98152;
- (e) a polynucleotide encoding the full-length protein encoded by the 30

cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

5 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

10 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

15 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

20 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801; the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421; the nucleotide sequence of the full-length protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152; or the nucleotide sequence of the mature protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152. In other preferred 25 embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112.

30 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:23.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:24;
- 5 (b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112;
- (c) fragments of the amino acid sequence of SEQ ID NO:24; and
- (d) the amino acid sequence encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

10 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:24 or the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 15 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886;
- 20 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101;
- 25 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101;
- 30 (h) a polynucleotide encoding the mature protein encoded by the

cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;

- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:26;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:26 having biological activity;
- 5 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- 10 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853; the nucleotide sequence of the full-length protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101.

20 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:25.

25 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:26;
- (b) fragments of the amino acid sequence of SEQ ID NO:26; and
- (c) the amino acid sequence encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;

30 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:26.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;
- 5 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483;
- 10 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101;
- 15 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101;
- 20 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- 25 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609; the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483; the nucleotide sequence of the full-length

protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101.

5 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:27.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the 10 group consisting of:

- (a) the amino acid sequence of SEQ ID NO:28;
- (b) fragments of the amino acid sequence of SEQ ID NO:28; and
- (c) the amino acid sequence encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101;

15 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:28.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

20 Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

25 The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

30 Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically

effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

#### BRIEF DESCRIPTION OF DRAWINGS

5 Fig. 1A and Fig. 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

Fig. 2 is an autoradiograph evidencing the expression of the following clone disclosed herein, BG33\_7.

10

#### DETAILED DESCRIPTION

##### ISOLATED PROTEINS AND POLYNUCLEOTIDES

15

20

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

25

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

##### Clone "AC41\_1"

30

A polynucleotide of the present invention has been identified as clone "AC41\_1".

AC41\_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC41\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC41\_1 protein").

The nucleotide sequence of AC41\_1 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC41\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 10 to 22 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 23, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC41\_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AC41\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AC41\_1 demonstrated at least some homology with sequences identified as L20319 (Rattus norvegicus developmentally regulated protein mRNA, complete cds), U46493 (Cloning vector pFlp recombinase gene, complete cds), and Z22650 (H.sapiens insertion polymorphism DNA). The predicted amino acid sequence disclosed herein for AC41\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AC41\_1 protein demonstrated at least some identity with sequences identified as L20319 (developmentally regulated protein [Rattus norvegicus]) and X12544 (3 HLA-DR B protein precursor (AA -29 to 267) [Homo sapiens]). Based upon homology, AC41\_1 proteins and each homologous protein or peptide may share at least some activity.

#### Clone "AC222\_1"

A polynucleotide of the present invention has been identified as clone "AC222\_1". AC222\_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No.

5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC222\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC222\_1 protein").

5 The nucleotide sequence of AC222\_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC222\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Amino acids 7 to 19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at 10 amino acid 20, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC222\_1 should be approximately 1400 bp.

15 The nucleotide sequence disclosed herein for AC222\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AC222\_1 demonstrated at least some homology with sequences identified as D10485 (Chicken mRNA for proteoglycan (PG-Lb) core protein, complete cds), D78274 (Mouse mRNA for proteoglycan, complete cds), N22463 (yw34c10.s1 Homo sapiens cDNA clone 254130 3'), U59111 (Human dermatan sulfate 20 proteoglycan 3 (DSPG3) mRNA, complete cds), U77127 (Bos taurus epiphycan mRNA, complete cds), and Z32693 (E.coli pT7hGH\_pl DNA, 6160bp). The predicted amino acid sequence disclosed herein for AC222\_1 was searched against the GenPept and GeneSeq 25 amino acid sequence databases using the BLASTX search protocol. The predicted AC222\_1 protein demonstrated at least some identity with sequences identified as D10485 (proteoglycan core protein [Gallus gallus]), D78274 (proteoglycan [Mus musculus]), U77127 (epiphycan [Bos taurus]), and U59111 (dermatan sulfate proteoglycan 3 [Homo sapiens]). Based upon homology, AC222\_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AJ143\_1"

30 A polynucleotide of the present invention has been identified as clone "AJ143\_1". AJ143\_1 was isolated from a human adult testes cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ143\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ143\_1 protein").

5

The nucleotide sequence of AJ143\_1 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AJ143\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 2 to 14 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 15, or are a transmembrane domain.

10

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ143\_1 should be approximately 1000 bp.

15

The nucleotide sequence disclosed herein for AJ143\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ143\_1 demonstrated at least some homology with sequences identified as T19431 (d08002s Homo sapiens cDNA clone d08002 5' end) and Z41997 (H. sapiens partial cDNA sequence; clone c-05c07); it may also show some similarity to phosphoenolpyruvate phosphomutase. Based upon homology, AJ143\_1 proteins and each homologous protein or peptide may share at least some activity.

20

#### Clone "AJ168\_4"

25

A polynucleotide of the present invention has been identified as clone "AJ168\_4". AJ168\_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ168\_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ168\_4 protein").

30

The nucleotide sequence of AJ168\_4 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the AJ168\_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ168\_4 should be approximately 700 bp.

5 The nucleotide sequence disclosed herein for AJ168\_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ168\_4 demonstrated at least some homology with sequences identified as T65223 (yc79c02.s1 Homo sapiens cDNA clone 22106 3'). Based upon homology, AJ168\_4 proteins and each homologous protein or peptide may share 10 at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AJ168\_4 protein sequence (SEQ ID NO:8).

#### Clone "AK684\_1"

15 A polynucleotide of the present invention has been identified as clone "AK684\_1". AK684\_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AK684\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also 20 referred to herein as "AK684\_1 protein").

The nucleotide sequence of AK684\_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AK684\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

25 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AK684\_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AK684\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AK684\_1 demonstrated at least some homology with sequences identified as AA226405 (nc20c05.r1 NCI CGAP Pr1 Homo sapiens cDNA 30 clone 2817), G15531 (human STS SHGC-17023), and T68858 (yc30d08.s1 Homo sapiens

cDNA clone 82191 3' similar to contains MSR1 repetitive element). Based upon homology, AK684\_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AK684\_1 protein sequence centered around amino acid 20 of SEQ ID NO:10.

5

Clone "AS209\_1"

10

A polynucleotide of the present invention has been identified as clone "AS209\_1". AS209\_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AS209\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS209\_1 protein").

15

20

The nucleotide sequence of AS209\_1 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AS209\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 32 to 44 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 45, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS209\_1 should be approximately 2882 bp.

25

30

The nucleotide sequence disclosed herein for AS209\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AS209\_1 demonstrated at least some homology with sequences identified as AA055217 (zf17h02.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 377235 3') and H29533 (ym60h11.r1 Homo sapiens cDNA clone 52955 5' similar to SP:A60164 S34329; PLATELET MEMBRANE GLYCOPROTEIN V PRECURSOR). The predicted amino acid sequence disclosed herein for AS209\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AS209\_1 protein demonstrated at least some

5

identity with sequences identified as D63875 (ORF [Homo sapiens]) and X53959 (slit protein [Drosophila melanogaster]). Based upon homology, AS209\_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AS209\_1 protein sequence, centered around amino acids 32, 387, 449, and 538 of SEQ ID NO:12.

10

Clone "AX56\_28"

A polynucleotide of the present invention has been identified as clone "AX56\_28". AX56\_28 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX56\_28 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX56\_28 protein").

15

The nucleotide sequence of AX56\_28 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX56\_28 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14.

20

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX56\_28 should be approximately 4500 bp.

25

The nucleotide sequence disclosed herein for AX56\_28 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX56\_28 demonstrated at least some homology with sequences identified as M20816 (Chicken cytотactин mRNA, partial cds, clone pEC803 [Gallus gallus]), N67571 (yz42a06.s1 Homo sapiens cDNA clone 285682 3'), and T19080 (e05023t Testis 1 Homo sapiens cDNA clone e05023 5' end). The predicted amino acid sequence disclosed herein for AX56\_28 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AX56\_28 protein demonstrated at least some identity with sequences identified as L12018 (putative protein [Caenorhabditis elegans]). Based upon homology, AX56\_28 proteins and each homologous protein or peptide may share at least some activity. The

30

TopPredII computer program predicts a potential transmembrane domain within the AX56\_28 protein sequence (SEQ ID NO:14).

Clone "AX92\_3"

5 A polynucleotide of the present invention has been identified as clone "AX92\_3". AX92\_3 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX92\_3 is a full-length 10 clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX92\_3 protein").

15 The nucleotide sequence of AX92\_3 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX92\_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Amino acids 13 to 25 are a predicted 20 leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 26, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX92\_3 should be approximately 1800 bp.

25 The nucleotide sequence disclosed herein for AX92\_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX92\_3 demonstrated at least some homology with sequences identified as AA003356 (mg49g01.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 427152 5'), AA036247 (mi74a03.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 472300 5'), F19608 (H.sapiens mitochondrial EST sequence (009-X4-35) from skeletal muscle), M10546 (Human mitochondrial DNA, fragment M1, encoding transfer RNAs, cytochrome oxidase I, and 2 URFs [Mitochondrion Homo sapiens]), and U46493 (Cloning vector pFlp recombinase gene, complete cds). Based upon homology, AX92\_3 proteins and each homologous protein or peptide may 30 share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AX92\_3 protein sequence, centered around amino

acids 20, 183, 269, and 295 of SEQ ID NO:16.

Clone "BF245\_1"

A polynucleotide of the present invention has been identified as clone "BF245\_1". BF245\_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BF245\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BF245\_1 protein").

The nucleotide sequence of the 5' portion of BF245\_1 as presently determined is reported in SEQ ID NO:17. An additional internal nucleotide sequence from BF245\_1 as presently determined is reported in SEQ ID NO:18. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:19. Amino acids 18 to 30 of SEQ ID NO:19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 31, or are a transmembrane domain. Additional nucleotide sequence from the 3' portion of BF245\_1, including the polyA tail, is reported in SEQ ID NO:20.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BF245\_1 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for BF245\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BF245\_1 demonstrated at least some homology with sequences identified as AA001743 (zh86h02.s1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 428211 3' similar to SW YY02\_HUMAN P42285 HYPOTHETICAL MYELOID CELL LINE PROTEIN 2), D29641 (Human mRNA for KIAA0052 gene, partial cds), Q92779 (Human thymopoietin continuous gene fragment), and R39256 (yc91h04.s1 Homo sapiens cDNA clone 23509 3'). The predicted amino acid sequence disclosed herein for BF245\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BF245\_1 protein

demonstrated at least some identity with sequences identified as Z70271 (W08D2.7 [Caenorhabditis elegans]). Based upon homology, BF245\_1 proteins and each homologous protein or peptide may share at least some activity.

5 Clone "BG33\_7"  
A polynucleotide of the present invention has been identified as clone "BG33\_7". BG33\_7 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer  
10 analysis of the amino acid sequence of the encoded protein. BG33\_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG33\_7 protein").

15 The nucleotide sequence of BG33\_7 as presently determined is reported in SEQ ID NO:21. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BG33\_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BG33\_7 should be approximately 900 bp.

20 The nucleotide sequence disclosed herein for BG33\_7 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BG33\_7 demonstrated at least some homology with sequences identified as AA033818 (zf02c08.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 375758 3') and AA462657 (vg68e04.r1 Soares mouse NbMH Mus musculus cDNA clone 871134 5'). Based upon homology, BG33\_7 proteins and each  
25 homologous protein or peptide may share at least some activity.

Fig. 2 is an autoradiograph evidencing expression in COS cells of clone BG33\_7 of the present invention.

30 Clone "BM46\_10"  
A polynucleotide of the present invention has been identified as clone "BM46\_10". BM46\_10 was isolated from a human adult muscle cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BM46\_10 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BM46\_10 protein").

The nucleotide sequence of BM46\_10 as presently determined is reported in SEQ ID NO:23. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BM46\_10 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:24.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BM46\_10 should be approximately 3600 bp.

The nucleotide sequence disclosed herein for BM46\_10 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BM46\_10 demonstrated at least some homology with sequences identified as F19321 (H.sapiens EST sequence 008-X (391 nt)), N79027 (zb43c09.s1 Homo sapiens cDNA clone 306352 3'), U46493 (Cloning vector pFlp recombinase gene, complete cds), and W74198 (zd74d05.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 346377 3'). Based upon homology, BM46\_10 proteins and each homologous protein or peptide may share at least some activity.

Clone "J317\_1"  
A polynucleotide of the present invention has been identified as clone "J317\_1". J317\_1 was isolated from a human peripheral blood mononuclear cells (treated with phytohemagglutinin and phorbol myristate acetate and mixed lymphocyte reaction) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. J317\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J317\_1 protein").

The nucleotide sequence of J317\_1 as presently determined is reported in SEQ ID NO:25. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the J317\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:26. Amino acids 19 to 31 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 32, or are a transmembrane domain.

5 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone J317\_1 should be approximately 1300 bp.

10 The nucleotide sequence disclosed herein for J317\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. J317\_1 demonstrated at least some homology with sequences identified as N21491 (yx58f09.s1 Homo sapiens cDNA clone 265961 3'), R39024 (yd08h03.s1 Homo sapiens cDNA clone 25214 3'), T93953 (ye06h06.r1 Homo sapiens cDNA clone 116987 5' similar to contains HGR repetitive element), and Z25379 (H. sapiens partial cDNA sequence; clone C6F07; version 1; strand(+), single read). Based upon homology, J317\_1 proteins and each homologous protein or peptide may share 15 at least some activity.

#### Clone "O289\_1"

20 A polynucleotide of the present invention has been identified as clone "O289\_1". O289\_1 was isolated from a human adult blood (dendritic cells) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. O289\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "O289\_1 protein").

25 The nucleotide sequence of O289\_1 as presently determined is reported in SEQ ID NO:27. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the O289\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:28.

30 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone O289\_1 should be approximately 700 bp.

The nucleotide sequence disclosed herein for O289\_1 was searched against the

GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. O289\_1 demonstrated at least some homology with sequences identified as H59298 (yr04c07.r1 Homo sapiens cDNA clone 204300 5' similar to contains MER22 repetitive element). Based upon homology, O289\_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a large potential transmembrane domain within the O289\_1 protein sequence, centered around amino acid 35 of SEQ ID NO:28. The nucleotide/amino acid sequence of O289\_1 indicates that it may contain MER transposon repetitive elements.

10

Deposit of Clones

15

Clones AC41\_1, AC222\_1, AJ143\_1, AJ168\_4, AK684\_1, AS209\_1, AX92\_3, BF245\_1, BG33\_7, J317\_1 and O289\_1, along with AX56\_8 and BM46\_3 (additional isolates of clones AX56\_28 and BM46\_10, respectively), were deposited on July 9, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98101, from which each clone comprising a particular polynucleotide is obtainable. AX56\_28 was deposited on September 26, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98180; BM46\_10 was deposited on August 23, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98152. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

20

25

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1A or Fig. 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from

30

pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the *Clal* site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

10 Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

15 An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

	<u>Clone</u>	<u>Probe Sequence</u>
20	AC41_1	SEQ ID NO:29
	AC222_1	SEQ ID NO:30
	AJ143_1	SEQ ID NO:31
	AJ168_4	SEQ ID NO:32
	AK684_1	SEQ ID NO:33
	AS209_1	SEQ ID NO:34
25	AX56_28	SEQ ID NO:35
	AX92_3	SEQ ID NO:36
	BF245_1	SEQ ID NO:37
	BG33_7	SEQ ID NO:38
	BM46_10	SEQ ID NO:39
30	J317_1	SEQ ID NO:40
	O289_1	SEQ ID NO:41

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoamidite residue rather than a nucleotide (such as, for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).

5 The design of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- 10 (b) It should be designed to have a  $T_m$  of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-<sup>32</sup>P ATP (specific activity 6000 Ci/mmol) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

20 The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu$ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100  $\mu$ g/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100  $\mu$ g/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

25 Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

30 The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0

with NaOH) containing 0.5% SDS, 100  $\mu$ g/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then 5 preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 10 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

15 Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules 20 such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion 25 would generate a decavalent form of the protein of the invention.

30 The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be

determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which the cDNA sequences are derived and any contiguous regions of the genome necessary for the regulated expression of such genes, including but not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

5 The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides .

10 The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

15 The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

5

10

15

20

25

30

35

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) <sup>†</sup>	Hybridization Temperature and Buffer <sup>†</sup>	Wash Temperature and Buffer <sup>†</sup>
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	< 50	T <sub>B</sub> *; 1xSSC	T <sub>B</sub> *; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	< 50	T <sub>D</sub> *; 1xSSC	T <sub>D</sub> *; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	< 50	T <sub>F</sub> *; 1xSSC	T <sub>F</sub> *; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	< 50	T <sub>H</sub> *; 4xSSC	T <sub>H</sub> *; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	< 50	T <sub>J</sub> *; 4xSSC	T <sub>J</sub> *; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	< 50	T <sub>L</sub> *; 2xSSC	T <sub>L</sub> *; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	< 50	T <sub>N</sub> *; 6xSSC	T <sub>N</sub> *; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	< 50	T <sub>P</sub> *; 6xSSC	T <sub>P</sub> *; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	< 50	T <sub>R</sub> *; 4xSSC	T <sub>R</sub> *; 4xSSC

<sup>†</sup>: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

<sup>†</sup>: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

\*T<sub>B</sub> - T<sub>R</sub>: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T<sub>m</sub>) of the hybrid, where T<sub>m</sub> is determined according to the following equations. For hybrids less than 18 base pairs in length, T<sub>m</sub>(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T<sub>m</sub>(°C) = 81.5 + 16.6(log<sub>10</sub>[Na<sup>+</sup>]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na<sup>+</sup>] is the concentration of sodium ions in the hybridization buffer ([Na<sup>+</sup>] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such

as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or

thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope.

5 One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein.

10 The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

15 The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

20 25 The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or

replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity 5 of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be 10 encompassed by the present invention.

### USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays 15 cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

#### Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either 20 constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a 25 source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel 30

polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., *Cell* 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

5 Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

10

Cytokine and Cell Proliferation/Differentiation Activity

15 A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell 20 proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

25 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et 30 al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-

3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

5 Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon  $\gamma$ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

10 Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature* 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 15 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

20 Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro assays for Mouse Lymphocyte Function*; Chapter 6, *Cytokines and their cellular receptors*; Chapter 7, *Immunologic studies in Humans*); 25 Weinberger et al., *Proc. Natl. Acad. Sci. USA* 77:6091-6095, 1980; Weinberger et al., *Eur. J. Immun.* 11:405-411, 1981; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai 30

et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing

T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is 5 distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including 10 without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue 15 destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on 20 immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to 25 transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this manner prevents cytokine synthesis by immune 30 cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

30 The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy

in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, *Science* 257:789-792 (1992) and Turka *et al.*, *Proc. Natl. Acad. Sci USA*, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., *Fundamental Immunology*, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., *Fundamental Immunology*, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the

common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a

cytoplasmic-domain truncated portion) of an MHC class I  $\alpha$  chain protein and  $\beta_2$  microglobulin protein or an MHC class II  $\alpha$  chain protein and an MHC class II  $\beta$  chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In*

*vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

5 Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro assays for Mouse Lymphocyte Function* 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Bertagnolli et al., *J. Immunol.* 149:3778-3783, 1992.

10

15 Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., *J. Immunol.* 134:536-544, 1995; Inaba et al., *Journal of Experimental Medicine* 173:549-559, 1991; Macatonia et al., *Journal of Immunology* 154:5071-5079, 1995; Porgador et al., *Journal of Experimental Medicine* 182:255-260, 1995; Nair et al., *Journal of Virology* 67:4062-4069, 1993; Huang et al., *Science* 264:961-965, 1994; Macatonia et al., *Journal of Experimental Medicine* 169:1255-1264, 1989; Bhardwaj et al., *Journal of Clinical Investigation* 94:797-807, 1994; and Inaba et al., *Journal of Experimental Medicine* 172:631-640, 1990.

20

25 Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., *Cytometry* 13:795-808, 1992; Gorczyca et al., *Leukemia* 7:659-670, 1993; Gorczyca et al., *Cancer Research* 53:1945-1951, 1993; Itoh et al., *Cell* 66:233-243, 1991; Zacharchuk, *Journal of Immunology* 145:4037-4045, 1990; Zama et al., *Cytometry* 14:891-897, 1993; Gorczyca et al., *International Journal of Oncology* 1:639-648, 1992.

30 Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., *Blood* 84:111-117, 1994; Fine et al., *Cellular Immunology* 155:111-122, 1994; Galy et al., *Blood*

85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

### Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include,

without limitation, those described in: Johansson et al. *Cellular Biology* 15:141-151, 1995; Keller et al., *Molecular and Cellular Biology* 13:473-486, 1993; McClanahan et al., *Blood* 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., *Proc. Natl. Acad. Sci. USA* 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., *Experimental Hematology* 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

20 Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

25 A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. 30 *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also

is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of

central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon);

International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium ).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), 5 Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

#### Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin  $\alpha$  family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- $\beta$  group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

30

#### Chemotactic/Chemokinetic Activity

5           A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

10           A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

15           The activity of a protein of the invention may, among other means, be measured by the following methods:

20           Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

30           Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity.

As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., *J. Clin. Pharmacol.* 26:131-140, 1986; Burdick et al., *Thrombosis Res.* 45:413-419, 1987; Humphrey et al., *Fibrinolysis* 5:71-79 (1991); Schaub, *Prostaglandins* 35:467-474, 1988.

#### 15 Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek,

D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

5 **Anti-Inflammatory Activity**

Proteins of the present invention may also exhibit anti-inflammatory activity.

10 The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or 15 promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's 20 disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

25 **Cadherin/Tumor Invasion Suppressor Activity**

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human 30 diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to generate

5                   antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

10                  Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

15                  Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

20                  Tumor Inhibition Activity

25                  In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

30                  Other Activities

                        A protein of the invention may also exhibit one or more of the following

additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue 5 pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination 10 of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or 15 endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or 20 entity which is cross-reactive with such protein.

### ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including 25 without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not 30 interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The

pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a

liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection.

5 Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

20 When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01  $\mu$ g to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1  $\mu$ g to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful

therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous

5 cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or 10 additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. 15 Such matrices may be formed of materials presently in use for other implanted medical 20 applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential 25 matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure 30 proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of

the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

5 Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

10 A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor 15 cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

20 In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors 25 (TGF- $\alpha$  and TGF- $\beta$ ), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

30 The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering

various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage  
5 may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

10 Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, 15 without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

20 Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:
  - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 179 to nucleotide 742;
  - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568;
  - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101;
  - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;
  - (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101;
  - (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;
  - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
  - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
  - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
  - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
  - (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.
3. A host cell transformed with a composition of claim 2.
4. The host cell of claim 3, wherein said cell is a mammalian cell.
5. A process for producing a protein, which comprises:
  - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
  - (b) purifying the protein from the culture.
6. A protein produced according to the process of claim 5.
7. The protein of claim 6 comprising a mature protein.
8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
  - (a) the amino acid sequence of SEQ ID NO:2;
  - (b) the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129;
  - (c) fragments of the amino acid sequence of SEQ ID NO:2; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;the protein being substantially free from other mammalian proteins.
9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 218 to nucleotide 1126;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;

- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:4;
- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131;
- (c) fragments of the amino acid sequence of SEQ ID NO:4; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994;

- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:6;
- (b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20;
- (c) fragments of the amino acid sequence of SEQ ID NO:6; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Thr	Gly	Leu	His	Leu	Ser	Thr	Val	Glu	Ile	Ser	Ala	Ser	Phe	Cys	Lys
1															15
Pro	Leu	Leu	Arg	Thr	Leu	Ser	Cys	Leu	Gln	Lys	Ser	Leu	Ala	Leu	Thr
															30
Asp	Ser	Ala	Thr	Met	Trp	Leu	Tyr	Ser	Leu	Ile	Asn	Leu	Val	Leu	
															45
35								40							

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 308 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TTTTTTNGGA	ATCACCAAAA	TCAAGNGNGA	TATTGTGTTT	GCTGCCAGCC	TNNANTTGTA	60
GAGTCAGCTA	AAGGAATGTG	NGATTAA	TTATTGACCA	CCTGTTGAT	TACAGTTGAN	120
NACAAATGCC	TGCAAGTGTG	GATTGGTTT	TCCCANACAT	TTTAATATGT	ATTATATTAA	180
AATCAAACAT	CATTCATAGA	AAGCATATNA	CANANATGTT	TANACATAAG	CATNACATTT	240
TTTTAATAAA	AATGTANACA	GGTGGGGCAA	AAAAAAAAAA	AAAAAAAAAA	AAAAAAAAAA	300
AAAAAAAAAA						308

## (2) INFORMATION FOR SEQ ID NO:21:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 789 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ATTATGTCAT CCTTGCAGCC TTCACCCAAA GTTGCTCCCT CCTTCTAGGG CATTGGTTT	120
TCCTACTTAA TACCAAGTGT CAGCATGTTA GTAATAAACCA GGTGTCTCTA CCATTAGTCA	180
AAGGTGGGAG TTAAGCCTTT CATCTTGTA GCTTCTCCA GTACCTAACCC ATGATTTACT	240
TCATGGGAAG TCCCTCAAAG TACTATTAAT TATCCTGTGT TCTCCTGCCT TGCCCTTTAA	300
CAAAAATTCT GCTGTTCTG ATTATTTCCA TTTTACCAAG	339

## (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 552 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AAATANAAAT ANAACAAATT NTAGGGAAAGG ACTAAACTGT CTAAAGAAAT GTAAAATCCA	60
AAGACTTGGA TTTTCAACCT ATATCAGAAG ACACTTTTT TTCAGTTCCC ATGTGAAATT	120
CTTTNTAGGC CAAGGAAGGA CAAATACAAA TTTTGATTAC AAATTATTT TAGAACTTTG	180
ACACCTACAC TTAAATTCTG AGTCATTAAA CAGGCCTACA TTTATCAACT GTGGAAATAT	240
CAGCCAGTTT TTGCAAACCT CTTCTTAGGA CACTAAGTTG TTTGCAGAAA TCACTAGCAT	300
TGACTGACTC AGCAACAATG TGGTTATATT CTTTGATTAA CTTAGTCCTT TTTCTTGGTC	360
AAGAGTCAGT AGACAGGACT GAAGCTTATG CCCCTTGCCC CCCCACCACC ACTCCATTAC	420
TACCACCTTG GTTTAGCCAT CCTTTCTTG ATCTGTTCTC CCCACTTCTA CTGTGCTACT	480
CTACAGACTT GCCCTGAATG TAAGAGCAAC AATTACCTTG TAAAGTCCAA GTTGGGGCAG	540
GTCACTCCCC AA	552

## (2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 47 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

Gln Leu His Glu Tyr Ala His Arg Ala Cys Cys Gln Cys Arg Arg Asp  
 225 230 235 240  
 Ser Val Gln Thr Cys Gly Pro Val Arg Leu Leu Pro Ser Met Cys Cys  
 245 250 255  
 Glu Glu Ala Cys Ser Pro Asn Pro Ala Thr Leu Gly Cys Gly Val His  
 260 265 270  
 Ser Ala Ala Ser Leu Gln Ala Arg Asn Ala Gly Pro Ala Gly Glu Met  
 275 280 285  
 Val Pro Thr Phe Phe Gly Ser Leu Thr Gln Ser Ile Cys Gly Glu Phe  
 290 295 300  
 Ser Asp Ala Trp Pro Leu Met Gln Asn Pro Met Gly Gly Asp Asn Ile  
 305 310 315 320  
 Ser Phe Cys Asp Ser Tyr Pro Glu Leu Ala Gly Glu Asp Ile His Ser  
 325 330 335  
 Leu Asn Pro Glu Leu Glu Ser Ser Thr Ser Leu Asp Ser Asn Ser Ser  
 340 345 350  
 Gln Asp Leu Val Gly Gly Ala Val Pro Val Gln Ser His Ser Glu Asn  
 355 360 365  
 Phe Thr Ala Ala Thr Asp Leu Ser Arg Tyr Asn Asn Thr Leu Val Glu  
 370 375 380  
 Ser Ala Ser Thr Gln Asp Ala Leu Thr Met Arg Ser Gln Leu Asp Gln  
 385 390 395 400  
 Glu Ser Gly Ala Ile Ile His Pro Ala Thr Gln Thr Ser Leu Gln Val  
 405 410 415  
 Arg Gln Arg Leu Gly Ser Leu  
 420

## (2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 339 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GCAGGCCGCAG GTCTAGAATT CAATCGGGAG AGAGATACTG CCTGGTTCTT ACAGACACAG

60

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 423 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ala Leu Lys Val Leu Leu Glu Gln Glu Lys Thr Phe Phe Thr Leu  
1 5 10 15

Leu Val Leu Leu Gly Tyr Leu Ser Cys Lys Val Thr Cys Glu Thr Gly  
20 25 30

Asp Cys Arg Gln Gln Glu Phe Arg Asp Arg Ser Gly Asn Cys Val Pro  
35 40 45

Cys Asn Gln Cys Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe  
50 55 60

Gly Tyr Gly Glu Asp Ala Gln Cys Val Thr Cys Arg Leu His Arg Phe  
65 70 75 80

Lys Glu Asp Trp Gly Phe Gln Lys Cys Lys Pro Cys Leu Asp Cys Ala  
85 90 95

Val Val Asn Arg Phe Gln Lys Ala Asn Cys Ser Ala Thr Ser Asp Ala  
100 105 110

Ile Cys Gly Asp Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val  
115 120 125

Gly Phe Gln Asp Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro  
130 135 140

Tyr Glu Pro His Cys Ala Ser Lys Val Asn Leu Val Lys Ile Ala Ser  
145 150 155 160

Thr Ala Ser Ser Pro Arg Asp Thr Ala Leu Ala Val Ile Cys Ser  
165 170 175

Ala Leu Ala Thr Val Leu Leu Ala Leu Leu Ile Leu Cys Val Ile Tyr  
180 185 190

Cys Lys Arg Gln Phe Met Glu Lys Lys Pro Ser Trp Ser Leu Arg Ser  
195 200 205

Gln Asp Ile Gln Tyr Asn Gly Ser Glu Leu Ser Cys Leu Asp Arg Pro  
210 215 220

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTCGACGGGA	ACGTAGAACT	CTCCAACAAT	AAATACATTT	GATAAGAAAG	ATGGCTTTAA	60
AAGTGCTACT	AGAACAAAGAG	AAAACGTTT	TCACTCTTT	AGTATTACTA	GGCTATTTGT	120
CATGTAAAGT	GACTTGTGAA	ACAGGAGACT	GTAGACAGCA	AGAATTCAAG	GATCGGTCTG	180
GAAACTGTGT	TCCCTGCAAC	CAGTGTGGC	CAGGCATGGA	GTTGTCTAAG	GAATGTGGCT	240
TCGGCTATGG	GGAGGATGCA	CAGTGTGTGA	CGTGCCGGCT	GCACAGGTT	AAGGAGGACT	300
GGGGCTTCCA	GAAATGCAAG	CCCTGTCTGG	ACTGCGCAGT	GGTGAACCGC	TTTCAGAAGG	360
CAAATTGTTTC	AGCCACCAAGT	GATGCCATCT	GCAGGGACTG	CTTGCCAGGA	TTTTATAGGA	420
AGACGAAACT	TGTCGGCTTT	CAAGACATGG	AGTGTGTGCC	TTGTGGAGAC	CCTCCTCCTC	480
CTTACGAACC	GCACTGTGCC	AGCAAGGTCA	ACCTCGTGAA	GATCGCGTCC	ACGGCCTCCA	540
GCCCACGGGA	CACGGCGCTG	GCTGCCGTIA	TCTGCAGCGC	TCTGGCCACC	GTCCTGCTGG	600
CCCTGCTCAT	CCTCTGTGTC	ATCTATTGTA	AGAGACAGTT	TATGGAGAAG	AAACCCAGCT	660
GGTCTCTGCG	GTCACAGGAC	ATTCAGTACA	ACGGCTCTGA	GCTGTCTGT	CTTGACAGAC	720
CTCAGCTCCA	CGAATATGCC	CACAGAGCCT	GCTGCCAGTG	CCGCCGTGAC	TCAGTGCAGA	780
CCTGCGGGCC	GGTGCCTTG	CTCCCACCCA	TGTGCTGTGA	GGAGGCCTGC	AGCCCCAAC	840
CGGCGACTCT	TGGTTGTGGG	GTGCATTCTG	CAGCCAGTCT	TCAGGCAAGA	AACGCAGGCC	900
CAGCCGGGGA	GATGGTGCCG	ACTTTCTCG	GATCCCTCAC	GCAGTCCATC	TGTGGCGAGT	960
TTTCAGATGC	CTGGCCTCTG	ATGCAGAAC	CCATGGGTGG	TGACAACATC	TCTTTTTGTG	1020
ACTCTTATCC	TGAACTCGCT	GGAGAAGACA	TTCATTCTCT	CAATCCAGAA	CTTGAAAGCT	1080
CAACGTCTTT	GGATTCAAAT	AGCAGTCAAG	ATTTGGTTGG	TGGGGCTGTT	CCAGTCCAGT	1140
CTCATTCTGA	AAACTTTACA	GCAGCTACTG	ATTTATCTAG	ATATAACAAAC	ACACTGGTAG	1200
AATCAGCATC	AACTCAGGAT	GCACTAAC	TGAGAAGCCA	GCTAGATCAG	GAGAGTGGCG	1260
CTATCATCCA	CCCAGCCACT	CAGACGTCCC	TCCAGGTAAG	GCAGCGACTG	GGTTCCCTGT	1320
GAACACAGCA	CTGACTTACA	GTAGATCAGA	ACTCTGTTCC	CAGCATAAGA	TTTGGGGAA	1380
CCTGATGAGT	TTTTTTTTG	CATCTTAAT	AATTCTTGT	ATGTTGTAGA	GTATGTTTA	1440
AAATAAATTT	CAAGTATTTT	TTTAAAAAC	TAACCAAC	AAACCAAC	AAACCAAC	1500
AA						1502

## (2) INFORMATION FOR SEQ ID NO:16:

- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Arg Leu Lys Met Phe Leu Thr Pro His Met Cys Val Met Ala Ser  
1 5 10 15

Leu Ile Cys Ser Arg Gln Leu Phe Gly Trp Leu Phe Arg Arg Val Arg  
20 25 30

Phe Glu Lys Val Ile Phe Gly Ile Leu Thr Val Met Ser Ile Gln Gly  
35 40 45

Tyr Ala Asn Leu Arg Asn Gln Trp Ser Ile Ile Gly Glu Phe Asn Asn  
50 55 60

Leu Pro Gln Glu Glu Leu Leu Gln Trp Ile Lys Tyr Ser Thr Thr Ser  
65 70 75 80

Asp Ala Val Phe Ala Gly Ala Met Pro Thr Met Ala Ser Ile Lys Leu  
85 90 95

Ser Thr Leu His Pro Ile Val Asn His Pro His Tyr Glu Asp Ala Asp  
100 105 110

Leu Arg Ala Arg Thr Lys Ile Val Tyr Ser Thr Tyr Ser Arg Lys Ser  
115 120 125

Ala Lys Glu Val Arg Asp Lys Leu Leu Glu Leu His Val Asn Tyr Tyr  
130 135 140

Val Leu Glu Glu Ala Trp Cys Val Val Arg Thr Lys Phe Ile Leu Gln  
145 150 155 160

Asp Gly Gln Glu Val Leu Ser Ala Ala Glu Lys  
165 170

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1502 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

AAAAGGTAAA TTACTTTCT GTTCATTGAA TGTCAGCCTT ATTAAGCTTG TCATATAAGT	3120
TATTAATCA TTCATGTCAT ACTGCATAAA CAAATGTTCA TTTCAGAATT TTAAAGAGAA	3180
ATGTATATAA AAGAACAAATG AATTTAATA AATCAGGGGT ATGTAAGTCC TTTTCATCC	3240
AACTAGGTGA ATTGCTTCAG ATTTCTCTA GTACCAGAGG GTACCTCCTC AAACCTTTG	3300
AACCACCTAA GGCAGAAGAA TGCAAGCTCT GAAATGACAT CCTTAAAATG CTGATACTGG	3360
TCACAGCCTC TTTACCTCTG TGAGGAAATT GTAACAGTGT GTCTTTAAG GTGTTTTAT	3420
TTTACCGGCC CTTAAGAAAG ATCTTTAATA CCTTTTAATA CTTTTTTA ATAATTCAA	3480
GTTGAAGTGT TTTAAAAAC ACTTTGTTT GTAATGTTT GAATCTCTG AGATGTGTTT	3540
ACCCCCTAG ATACATATTT GCCACTGGTT AGTTCTCCAT CTAAGCTCAA GAGGTTATT	3600
ATCTCTCTT AGATTCCAGT GGTTTTCTT TTAACATCCA GGTAAAATAG AAACGTCTAT	3660
GGTATACAAC CAAGTTTGG GGTTAAACAT AATCAGAAAA GAAAATCCAG TTAAATTAT	3720
GAAGTGAGAT TTTCAGATCC TAGATCTTGA ATAAAGGAAA GGTCTTTCA TCTTGATGGC	3780
CCCAAAGCTT GTTGATCATG GTCTTTATTT CTGGCCACTA TCTTCTTAAA TAATATATTT	3840
TTAACGCCCTC ATTTATTTT GTTTGGGT GAGGAAAGTC ATGTTTCTA AGTCCTCTCC	3900
CCTAATAAAA CCTACCAAC AATAGTCTT TGAAAAGTGG TAGTTATCTT GAAGATACTC	3960
TTGCCAAATG CAAAGATAAA CATTCTTTT GTCTGTTA TAAATATGAA ATATGCCAGA	4020
TCTGTAGTAT TTTAATGTGC ATCTACTTTA AATGAGTCAT CTTGGGGTTT TTATAATTCC	4080
CTTATGTTCT CGCCCCCTCTA CACTTGAAAT AACAAAATGC CTTAATTAA TGGATTAGTT	4140
CTCTTATAGT AGACAGGCAG CTATATGCAG CAAAACCAAT AAAGTTATTT TTCAACTTTC	4200
ATAGTTGTAA AATATTTAT AACAGAATAC AAAACAGCTA AGAAAACATG CCACATTAA	4260
TTTTAGCATT TTCAAATAAT TTGTTTTGG TGTAAGCACA GGATAAAAAA GGAGAGCGTC	4320
AAAGAAAAGA GACATAACAC CTAACATTCA TAAAAATTAA CAAAGTATAT TTTGGATGAT	4380
GTTTTTACAG GAAATATTTT AAATAAGTTG GTAGAACTTT TAAAATGGTA CTGTATTAGC	4440
TAATAAAATA TTCAGTACAA ATATATGTTT GGATTATGC ATTAAAAAAC TAATAAAATT	4500
ATTTCCAAT TTAAAAAAA AAAAAAAA A	4531

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 171 amino acids
- (B) TYPE: amino acid

GGATGAAGCA GGGTGA CTTG AGATTC AACT ATTCA GTATG CACA ATT TAAA ACT TAG	1440
GAATTGTTA TTTCTTGGAA CTTT CCGTTT AATGTTTTG GACTGCAGTT AGCCACAGGT	1500
AACTGAAACT GTGGAAAGTG AGGATTGGAG GATAAGCAGA GACTGTGGTA TTCATTTCAT	1560
TGCACAGTGC CTAAAATACA GTAGGTGTAC TATAAATATT TTGTAAAGGG ACAACTTTTC	1620
TGAAACTAAA AATATTTATG TTTTACCCAA TAATTTTCT TCTGGAAATT TATGCTAAGG	1680
AAATATTCAAG AGATGCTTAC AAAGTTTAT GCATGAGTGT CCATGTTATT TGTAAATTGTG	1740
AAAAATGAAA ATAAC TCAAAG AGTTAACAG TGGTCATCTA AAGTATTGTA TACACTGTAT	1800
ATATAGTTG AATAGAAGGT CATCCTATTC ATTTATTAAT GAGAGGTACA ATCTCTAGGG	1860
ATCTGTAAAA TCTATTTGT CTTAACCAAA GAACAAATT TTGACATATC TTGAATAGGA	1920
TGACTATAAA TTATGACTTT TAAATTGTTG TAATTTTGT ACTATTATCT GATATTTTA	1980
TTTTTATGTA TTTTCGTAAG TAGTTAGAG ATAGTCACAT TTTAAAATC TAAGATCAAG	2040
CAAATGAAGC TTATTTTAT GTATTCA TAG TATAAAAGAC CTTCA GTAAA TAGGTAATAT	2100
TTTTGTTTA TTCTAGAAAA CAGCTCCTTG AACACAGTGA GCTGGCTTTT CACACATTGC	2160
AGTTGTTAGT GTTTACTGCC CTTGCCATT TAAATTATGAG GCTAAAGATG TTTTGACAC	2220
CGCACATGTG TGTTATGGCT TCCTTGATAT GCTCTCGACA GCTCTTGCG TGGCTTTTC	2280
GCAGAGTCG TTTTGAGAAG GTTATCTTG GCATTTAAC AGTGATGTCA ATACAAGGTT	2340
ATGCAAACCT CCGTAATCAA TGGAGCATAA TAGGAGAATT TAATAATTTG CCTCAGGAAG	2400
AACTTTACA GTGGATCAA TACAGTACCA CATCAGATGC TGTCTTGCA GGTGCCATGC	2460
CTACAATGGC AAGCATCAAG CTGTCTACAC TTCATCCCAT TGTGAATCAT CCACATTACG	2520
AAGATGCAGA CTTGAGGGCT CGGACAAAAA TAGTTTATTC TACATATAGT CGAAAATCTG	2580
CCAAAGAAAGT AAGAGATAAA TTGTTGGAGT TACATGTGAA TTATTATGTT TTAGAAGAGG	2640
CATGGTGTGT TGTGAGAACT AAGTTTATAC TTCAAGATGG ACAAGAAGTT CTATCAGCTG	2700
CTGAGAAATG ATGCCAGATG GTAACTCAGA TATACAAGAA ATACTCAAAT GCGCTGGAAA	2760
TGGCCTGGTT GCAGTATGCT TGAAATCTGG GATGTGGAAG ACCCTTCCAA TGCA GCTAAC	2820
CCTCCCTTAT GTAGCGTCCT GCTCGAAGAC GCCAGGCCTT ACTTCACCAC AGTATTCAG	2880
AATAGTGTGT ACAGAGTATT GAAGGTTAAC TGAGAAGGAT ACTACCCATT TTACTATGGC	2940
ACAATGCCGT GTGTCAAAAAA CAATCACCCCT TTGGCTTATT CACATTAATA AAAATCACAA	3000
GCTTTAATAA CAGACACTTA AAAATAAGAT AAAATGGAT TGGAAATTTT TCTGATTACT	3060

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TTGCTCTTCA	ACTTTCTTT	GAGGCTTAA	ATTAGGCAA	TATATTTTC	TTAGAATTTC	60
TGAAAACCTCC	TTTCACTGG	AGCTTATT	AATTATATGG	ATGCATTATC	CTCTTAAACT	120
TCTGTGAAAA	CAATAATTGG	AGTTTCATT	TGCATTGGCT	GTTCATGAG	AGGTCAAGCT	180
TTTGCTTAT	TTATTTGAT	GTTCCTTT	CATGATATCT	GTGTCTGGG	ATTTGGTTGT	240
ATATTCACAT	TTTAATTAG	CTACTTGATT	TAAATAAAAGT	ATCAGTAGTT	ACTTCAGGG	300
TTCTTGGTGA	TTATAATAAT	TACTCACCTA	CCAGGCTTCT	TCCTGCATG	CAGCTCACTA	360
CAGGAATCTG	TTGTGCCTAG	AAGATTCGG	GACAAGTGG	GAAACCCAC	TCCGTTAACT	420
GCATACACAG	GGAAGGGAGCT	ATGAGGGAGA	CAGAATAATT	TGGTCTCTAC	TATTACCTTA	480
AGAGACCTTC	CCCTGTCTTC	GATTAAAAAA	AAAACACTG	CATACAAAGG	GTAGGAGCTA	540
CAAGGGACAT	AGAATAATT	GGACTCCATT	ACTACCTTAA	GAGACCTTCC	CCTGACTTCT	600
CTTTTAAAAAA	ACCTATGAGT	CTCTGTACCC	CTGAACTTAC	TTTCCACACC	TATTTCTCTC	660
TTCACCCCCA	AAATCCATAT	TAGAATGCC	CTGCAGGCTA	AAAGCCTTT	CATAAAAGTA	720
AAATACCCAG	TCTTTCAAG	AGAACAAATAA	AATAGGCAGT	CTCCTACCTC	TTGTCTTACT	780
CTAATATAAA	CTCCATGAAG	ATAAGTATTG	TATCCATACT	GTTCATGCTG	CACAGCAGTT	840
GCCCTTATCT	GCAGGGCGAC	GCATCCAAG	ACCCCCAGTG	GATGCTTGAA	ACTGCAGAGA	900
GTAACACACG	TGATTGCCAC	CATCGGAACA	CATTCTGTT	CACGTCTTCC	ACCCACAGAT	960
TTAATGCCTT	TTCCATCTTA	ACTAAGCACT	CATCATGGAC	TGTGGCCATA	ACTTTGCAG	1020
TTTTAGATGC	AACAGAAAAA	CTAACATTAA	TTTTTCTTC	TTCTTCACAA	TTTCATGGGT	1080
AGATTGTT	TTACCGTACA	TCTTAGCAAC	CTCAGCATAT	GATGTTTTT	CTTTGAGAA	1140
CTTTCACCTT	TTCTCTAAA	GAAATCACTT	TACAGCTTCT	CTTTGGCATA	TCTCAACTGC	1200
CAGCATCACT	GCTCTTGAAC	TTGGGGCCA	TTATTAAGTC	AAAAGAGGGT	TACTTCAAAA	1260
CAAGCACTGA	GATACCACCA	GAGTCCATCT	GATAACTAAG	ATGGTAACTA	CATGACTAAC	1320
AGGCCGGTGA	CGTATAAAGC	ATGGATATGC	TGGACAAAGG	GGTAGTCAT	ATCCCAGGTA	1380

Ser Trp Ile Thr Pro Asn Gly Thr Val Met Thr His Gly Ala Tyr Lys  
 385 390 395 400  
 Val Arg Ile Ala Val Leu Ser Asp Gly Thr Leu Asn Phe Thr Asn Val  
 405 410 415  
 Thr Val Gln Asp Thr Gly Met Tyr Thr Cys Met Val Ser Asn Ser Val  
 420 425 430  
 Gly Asn Thr Thr Ala Ser Ala Thr Leu Asn Val Thr Ala Ala Thr Thr  
 435 440 445  
 Thr Pro Phe Ser Tyr Phe Ser Thr Val Thr Val Glu Thr Met Glu Pro  
 450 455 460  
 Ser Gln Asp Glu Ala Arg Thr Thr Asp Asn Asn Val Gly Pro Thr Pro  
 465 470 475 480  
 Val Val Asp Trp Glu Thr Thr Asn Val Thr Thr Ser Leu Thr Pro Gln  
 485 490 495  
 Ser Thr Arg Ser Thr Glu Lys Thr Phe Thr Ile Pro Val Thr Asp Ile  
 500 505 510  
 Asn Ser Gly Ile Pro Gly Ile Asp Glu Val Met Lys Thr Thr Lys Ile  
 515 520 525  
 Ile Ile Gly Cys Phe Val Ala Ile Thr Leu Met Ala Ala Val Met Leu  
 530 535 540  
 Val Ile Phe Tyr Lys Met Arg Lys Gln His His Arg Gln Asn His His  
 545 550 555 560  
 Ala Pro Thr Arg Thr Val Glu Ile Ile Asn Val Asp Asp Glu Ile Thr  
 565 570 575  
 Gly Asp Thr Pro Met Glu Ser His Leu Pro Met Pro Ala Ile Glu His  
 580 585 590  
 Glu His Leu Asn His Tyr Asn Ser Tyr Lys Ser Pro Phe Asn His Thr  
 595 600 605  
 Thr Thr Val Asn Thr Ile Asn Ser Ile His Ser Ser Val His Glu Pro  
 610 615 620  
 Leu Leu Ile Arg Met Asn Ser Lys Asp Asn Val Gln Glu Thr Gln Ile  
 625 630 635 640

## (2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4531 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double

85	90	95
Lys His Leu Arg His Leu Glu Ile Leu Gln Leu Ser Arg Asn His Ile		
100	105	110
Arg Thr Ile Glu Ile Gly Ala Phe Asn Gly Leu Ala Asn Leu Asn Thr		
115	120	125
Leu Glu Leu Phe Asp Asn Arg Leu Thr Thr Ile Pro Asn Gly Ala Phe		
130	135	140
Val Tyr Leu Ser Lys Leu Lys Glu Leu Trp Leu Arg Asn Asn Pro Ile		
145	150	155
Glu Ser Ile Pro Ser Tyr Ala Phe Asn Arg Ile Pro Ser Leu Arg Arg		
165	170	175
Leu Asp Leu Gly Glu Leu Lys Arg Leu Ser Tyr Ile Ser Glu Gly Ala		
180	185	190
Phe Glu Gly Leu Ser Asn Leu Arg Tyr Leu Asn Leu Ala Met Cys Asn		
195	200	205
Leu Arg Glu Ile Pro Asn Leu Thr Pro Leu Ile Lys Leu Asp Glu Leu		
210	215	220
Asp Leu Ser Gly Asn His Leu Ser Ala Ile Arg Pro Gly Ser Phe Gln		
225	230	235
Gly Leu Met His Leu Gln Lys Leu Trp Met Ile Gln Ser Gln Ile Gln		
245	250	255
Val Ile Glu Arg Asn Ala Phe Asp Asn Leu Gln Ser Leu Val Glu Ile		
260	265	270
Asn Leu Ala His Asn Asn Leu Thr Leu Leu Pro His Asp Leu Phe Thr		
275	280	285
Pro Leu His His Leu Glu Arg Ile His Leu His His Asn Pro Trp Asn		
290	295	300
Cys Asn Cys Asp Ile Leu Trp Leu Ser Trp Trp Ile Lys Asp Met Ala		
305	310	315
Pro Ser Asn Thr Ala Cys Cys Ala Arg Cys Asn Thr Pro Pro Asn Leu		
325	330	335
Lys Gly Arg Tyr Ile Gly Glu Leu Asp Gln Asn Tyr Phe Thr Cys Tyr		
340	345	350
Ala Pro Val Ile Val Glu Pro Pro Ala Asp Leu Asn Val Thr Glu Gly		
355	360	365
Met Ala Ala Glu Leu Lys Cys Arg Ala Ser Thr Ser Leu Thr Ser Val		
370	375	380

TTTCTCTTAC	TTTCAACCG	TCACAGTAGA	GACTATGGAA	CCGTCTCAGG	ATGAGGCACG	2220
GACCACAGAT	AACAATGTGG	GTCCCACCTCC	AGTGGTCGAC	TGGGAGACCA	CCAATGTGAC	2280
CACCTCTCTC	ACACCACAGA	GCACAAGGTC	GACAGAGAAA	ACCTTCACCA	TCCCAGTGAC	2340
TGATATAAAC	ACTGGGATCC	CAGGAATTGA	TGAGGTCATG	AAGACTACCA	AAATCATCAT	2400
TGGGTGTTT	GTGCCATCA	CACTCATGGC	TGCAGTGATG	CTGGTCATTT	TCTACAAGAT	2460
GAGGAAGCAG	CACCATCGGC	AAAACCATCA	CGCCCCAACAA	AGGACTGTTG	AAATTATTAA	2520
TGTGGATGAT	GAGATTACGG	GAGACACACC	CATGGAAAGC	CACCTGCCA	TGCCTGCTAT	2580
CGAGCATGAG	CACCTAAATC	ACTATAACTC	ATACAAATCT	CCCTTCAACC	ACACAACAAC	2640
AGTTAACACA	ATAAATTCAA	TACACAGTTC	AGTGCATGAA	CCGTTATTGA	TCCGAATGAA	2700
CTCTAAAGAC	AATGTACAAG	AGACTCAAAT	CTAAAACATT	TACAGAGTTA	CAAAAAACAA	2760
ACAATCAAAA	AAAAAGACAG	TTTATTAAAA	ATGACACAAA	TGACTGGCT	AAATCTACTG	2820
TTTCAAAAAA	GTGTCTTAC	AAAAAAAAA	A			2851

## (2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 640 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met	Leu	Asn	Lys	Met	Thr	Leu	His	Pro	Gln	Gln	Ile	Met	Ile	Gly	Pro
1						5			10			15			
Arg	Phe	Asn	Arg	Ala	Leu	Phe	Asp	Pro	Leu	Leu	Val	Val	Leu	Leu	Ala
						20			25			30			
Leu	Gln	Leu	Leu	Val	Val	Ala	Gly	Leu	Val	Arg	Ala	Gln	Thr	Cys	Pro
						35			40			45			
Ser	Val	Cys	Ser	Cys	Ser	Asn	Gln	Phe	Ser	Lys	Val	Ile	Cys	Val	Arg
						50			55			60			
Lys	Asn	Leu	Arg	Glu	Val	Pro	Asp	Gly	Ile	Ser	Thr	Asn	Thr	Arg	Leu
						65			70			75			80
Leu	Asn	Leu	His	Glu	Asn	Gln	Ile	Gln	Ile	Ile	Lys	Val	Asn	Ser	Phe

TAATTGGAGT TACTGGAAAA GCAAGAATAA CTTATGCGGA TTAACAATAT GGAAACATCC	540
TGAGACTACT TTGGAATCGC CATAAATTAA GTGGGTTCCA GTTTGCAAA CAGAGAAACG	600
GTCCATGAAC AATTTGCTAC AGGTATAAAG AAGTATCTGC AGAAATCCAG AGCACTTATT	660
AAACTTCTTT GAGTTTCTC AGGAAGATCA ATACAAGATG GAGAAATT TT ATTAAAGATTG	720
GCAAACGCAC TGCCTACTTA CAGCATAGAG ACCCCCAGTG GAGAGCTAGA CTGTTGAAT	780
TCCAGAAGGA CCAACACCCAG ATAAATTATG AATGTTGAAC AAGATGACCT TACATCCACA	840
GCAGATAATG ATAGGTCCCTA GTTTAACAG GGCCCTATTT GACCCCTGC TTGTGGTGCT	900
GCTGGCTCTT CAACTTCTTG TGGTGGCTGG TCTGGTGCAG GCTCAGACCT GCCCTCTGT	960
GTGCTCCTGC AGCAACCCAGT TCAGCAAGGT GATTGTGTT CGGAAAAAAC TGCGTGAGGT	1020
TCCGGATGGC ATCTCCACCA ACACACGGCT GCTGAACCTC CATGAGAAC AAATCCAGAT	1080
CATCAAAGTG AACAGCTTCA AGCACTTGAG ACACTTGGAA ATCCTACAGT TGAGTAGGAA	1140
CCATATCAGA ACCATTGAAA TTGGGGCTTT CAATGGTCTG GCGAACCTCA ACACTCTGGA	1200
ACTCTTGAC AATCGTCTTA CTACCATCCC GAATGGAGCT TTTGTATACT TGTCTAAACT	1260
GAAGGAGCTC TGGTTCGAA ACAACCCAT TGAAAGCATC CCTTCTTATG CTTTTAACAG	1320
AATTCCCTCT TTGCGCCGAC TAGACTTAGG GGAATTGAAA AGACTTCAT ACATCTCAGA	1380
AGGTGCCTTT GAAGGTCTGT CCAACTTGAG GTATTGAAAC CTTGCCATGT GCAACCTTCG	1440
GGAAATCCCT AACCTCACAC CGCTCATAAA ACTAGATGAG CTGGATCTTT CTGGGAATCA	1500
TTTATCTGCC ATCAGGCCTG GCTCTTCCA GGGTTGATG CACCTTCAAA AACTGTGGAT	1560
GATACAGTCC CAGATTCAAG TGATTGAACG GAATGCCTTT GACAACCTTC AGTCACTAGT	1620
GGAGATCAAC CTGGCACACA ATAATCTAAC ATTACTGCCT CATGACCTCT TCACTCCCTT	1680
GCATCATCTA GAGCGGATAC ATTTACATCA CAACCCTTGG AACTGTAAC GTGACATACT	1740
GTGGCTCAGC TGGTGGATAA AAGACATGGC CCCCTCGAAC ACAGCTTGTT GTGCCCGGTG	1800
TAACACTCCT CCCAATCTAA AGGGGAGGTA CATTGGAGAG CTCGACCAGA ATTACTTCAC	1860
ATGCTATGCT CCGGTGATTG TGGAGCCCC TGCAGACCTC AATGTCACTG AAGGCATGGC	1920
AGCTGAGCTG AAATGTCGGG CCTCCACATC CCTGACATCT GTATCTTGGAA TTACTCCAAA	1980
TGGAACAGTC ATGACACATG GGGCGTACAA AGTGCAGGATA GCTGTGCTCA GTGATGGTAC	2040
GTTAAATTTC ACAAAATGTA CTGTGCAAGA TACAGGCATG TACACATGTA TGGTGAGTAA	2100
TTCCGTTGGG AATACTACTG CTTCAAGCCAC CCTGAATGTT ACTGCAGCAA CCACTACTCC	2160

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met	Arg	Val	Ser	Phe	Gly	Ala	Asp	Val	Gly	Phe	Gly	Thr	Ile	Ala	Cys
1				5					10				15		
Asp	Cys	His	Ser	Leu	Ala	Val	Cys	Ile	Pro	Gln	Lys	Leu	Phe	Ser	Glu
				20			25				30				
Ser	Ser	Ser	Trp	Pro	Lys	Ser	Trp	Val	Ser	Phe	Thr	Val	Leu	Val	Ala
				35				40				45			
Asp	Tyr	Ser	Arg	Gln	Met	Arg	Asn	Ser							
				50			55								

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2851 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ATTTCGTACA	GTAGGAGATT	TCAACAACGT	GACAATATTC	TCTAGGCACT	TGGGCTCACT	60
GTCTGTAGCC	CCCACCCCCC	GCCTTCGCC	ACCTCCTTGC	TTCCCTACTC	CCCCTCTGCG	120
TTTTGCCTTT	GATGAGTTTT	TGGCTTACTT	TTTGGCGGAG	TCTCTGGAC	ACGTTTTGCG	180
TGGTGCTGGA	AGATCAGATA	CATGGAACCT	TTGAAAACGT	ATTATTTTC	TCCGATATGAA	240
CTTAAAAAAA	AATAAAAAGA	AGAAAAGAAA	ATAGAGTAGT	GCACGGCAAG	CTAGAGGATT	300
GTAAATTTTC	CTTGGTGAAC	TTTGAGGATC	CATAAAGAAG	AAATGGTTCT	CTTTACTGCG	360
AGGCTGCAAG	GTCACCCAAT	GAGAGAGGGG	CCAAATAAGC	TGGAACATCA	TCTAATACAC	420
TGAATGTAGC	CACTCTGTGT	CTTTGATTG	GAGAGTTAG	TCCATTACCA	TTCAATGCTA	480

Pro Pro His Pro Thr Pro  
35

## (2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1047 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AGGCATGCC	CCATAAAAGG	GCTCCTGAAG	CTCTTGTA	AGGGTCTGA	AAAGGCAGA	60
TGAGGGTGT	CTTGCGGCG	GATGTGGGT	TTGGGACAAT	TGCATGTGAT	TGTCATTCTT	120
TAGCTGTCTG	CATCCCACAG	AAACTTTTT	CTGAGTCTTC	CAGCTGGCCC	AAGTCCTGGG	180
TCTCTTTAC	TGTTCTTGT	GCTGACTACA	GTAGGCAGAT	GAGGAACCT	TAGTCAATCT	240
GGGAAAAC	ACTGACTAT	AAACAATCCT	AAATTGAAAG	AAGTGTATGG	CATTGGGGGG	300
TGGGTGT	GATACAGAGT	GGAGCCTGCA	AGTCACGCA	CCGGGAACCA	AACCCCACCT	360
AACTTGGACT	GGACGTCCTC	TTCCAGGGAA	TCCAGCCAGG	GCCAATTAGA	AATGTGTCTT	420
AAATTGGTGT	CAGGTACCA	AAAACAAAAA	CAGGATCCAT	GGGGGCCTGT	GAAACTTCGA	480
GTGCCATTCA	TGCTCGGTTC	AGTCATCTGA	CTCGTCAGGA	TGACCAGCAG	TGCTCCCTGT	540
AACTCGCCAT	TATCTGACCA	ATTACTGGAG	CTACTTTATA	ATGAGGCTTC	TGGAGCTACT	600
TTATAATGAG	GCTTCTGTTT	GCTGTCATGG	TGGGGAGTTT	GGAATTGTGG	CTTCTTGCCT	660
AACACCAATG	AGAGGACTTT	GGGACAAACC	CCCAGAGCCA	GGAGTGT	TTT GAGGCCTAGT	720
GGGGTTGGGA	ACAAAGGGTC	AAGTGTGAG	GGAGTGGGA	AATTATGGGT	TGGGGACAGG	780
TGTGAACAGT	GGGCTTGGGG	GTGGCCCAAG	AGTACTAGAC	CAGAGAGGTC	CAGTGCCACC	840
CGCAGCCTGC	AGTGATACTA	GACAGGGGC	GGCTGTGTGG	AACCACAGAT	GACATCCCTT	900
CTCCTCTTGA	TGGAAGTGG	GGCTGCATCT	GAGAGCTTCC	CAGCCTAGAT	TCTGGTGGCT	960
GCATCTGAGA	GCTTCCCAGC	CTAGATTCTG	GTGGGATTGG	ATCTGGGAGG	GGGAAGACCC	1020
CAAAAAGCAA						AAAAAAA

## (2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 643 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAAAGAGGAG	CTGGCGGGG	TGGGGGAAG	GCGGAGGCAG	TYTAGTAATG	TAAAGCTCCG	60
CTGAGAGGGA	GAGTGCCGCC	CTAACACCTC	ATGCTGCCAG	TCCCCAAAG	ACTTCATTCA	120
TTCAACATAT	ATGTGACCGC	CTGCTACGTG	CCAGGCGTGG	GCCAGGTCT	AGGGACAAAG	180
GAGAGGCCTC	CGCACCCAC	CCCATGACCC	ATACCTCCTC	TTCCCCACCT	CCCTGGGCCA	240
GCCTGCCTTC	CTTCTCCCTC	CTCCTCCTTC	CTGGGGGAAG	GAAGCCCCAC	CTTCTGTGCG	300
CAGTCAGCTC	CTAAGCACGC	TCCCCTTCC	CCTGGCCTCC	CCATTTAAAAA	AGGGAGGCAA	360
AGGATGTCAC	CACTGTCACT	ACACTCATGG	CTTGCTCTG	GGAAGTCCTG	CAAATAAAAT	420
GAAAGTTCTC	CAACCCCTCC	MTACCCAYTC	GGGCCACAAA	GGCGAGGGGA	GGCAGGTYTG	480
AGGCAGAGGA	GCCAGGGCAG	GTGCGGCAGT	TCCGCYTCTG	GTCCCAAAGC	AAAGAKTCCC	540
CCTGTGACTG	ACAGCCCGTG	TTATGTTAAA	TACATTTGT	TGGTTTGTAA	TTCAAATCCC	600
ATAAAGCAGG	AGGTAGAGAG	CCAAAAAAA	AAAAAAA	AAA		643

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met	Leu	Pro	Val	Pro	Lys	Arg	Leu	His	Ser	Phe	Asn	Ile	Tyr	Val	Thr
1															15
Ala	Cys	Tyr	Val	Pro	Gly	Val	Gly	Gln	Val	Leu	Gly	Thr	Lys	Glu	Arg
														30	
20															

ACCCCAGCYT TCCGGCCACC ACAACAAAGA GCCGCWCCGA CCGGCGAGGA TWAACAGCGG	420
CGGAGGGCGA KAGGGCGGCG GGGCGAGCGC CTCCACGCAG CAACTCCGGA GTCCCCCGCT	480
TGCCCGAGCG CAGTTCTCC GCTGCTGTT CCACCGGCTT TGTAACACTG GGAATTTACA	540
TCCTCACCCG CACCCCTCAC GCCCGAGGAT TTTAAACTCA CCTTTACTCT CGAACTGAGA	600
GTTGCGGTAG ATGGGATTTT TGCCTTTCC CCAGATGGTT GAAGGTTAAG ATTTTGAA	660
ACCCCMCCAC CTCCTTATTT CTATTATTAT TTCTGCAAGA AAAGTATAAA GAGAGTTGTA	720
GTGGAGGTGA GATTGTGAT CGGGAAAGCC TTGCACTCCC TCCTTCTCCG TCTCCGCYT	780
CTCTCTCTCT GATTAGTTCC TATCCAGCAG CAGATTGAAG CAGGAGATGA TTCTTCTCAA	840
GGTTTGTCA GCAGCTTCAC TTCTAGGCGA AGGCTTCATG AACCAAGTGA CGTCAACCAA	900
CAAGGCTTCT CTCTCTCTCC TCTCTCTAAC AATGAAAGTT GCTGTTAACAA AGGGAAAAAA	960
AGAGAGAGAA TTGTTTATAC CATTTCAGTT CCAATAATAA AKGACCTATC AGYTCCTAAA	1020
GGAGCCAAAA AANANAAAANA AAAAAAAA AANAAGANAA GNNNNNAAAA AAANAAAAAA	1080
<b>AAA</b>	1083

## (2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 56 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Ile Leu Leu Lys Val Cys Ser Ala Ala Ser Leu Leu Gly Glu Gly			
1	5	10	15
Phe Met Asn Gln Val Thr Ser Thr Asn Lys Ala Ser Leu Ser Leu Leu			
20	25	30	
Ser Leu Thr Met Lys Val Ala Val Asn Lys Gly Lys Lys Glu Arg Glu			
35	40	45	
Leu Phe Ile Pro Phe Gln Phe Gln			
50	55		

## (2) INFORMATION FOR SEQ ID NO:7:

180	185	190
Leu Arg Glu Leu Val Leu Arg Asp Asn Lys Ile Arg Gln Leu Pro Glu		
195	200	205
Leu Pro Thr Thr Leu Thr Phe Ile Asp Ile Ser Asn Asn Arg Leu Gly		
210	215	220
Arg Lys Gly Ile Lys Gln Glu Ala Phe Lys Asp Met Tyr Asp Leu His		
225	230	235
His Leu Tyr Leu Thr Asp Asn Asn Leu Asp His Ile Pro Leu Pro Leu		
245	250	255
Pro Glu Asn Leu Arg Ala Leu His Leu Gln Asn Asn Asn Ile Leu Glu		
260	265	270
Met His Glu Asp Thr Phe Cys Asn Val Lys Asn Leu Thr Tyr Ile Arg		
275	280	285
Lys Ala Leu Glu Asp Ile Arg Leu Asp Gly Asn Pro Ile Asn Leu Ser		
290	295	300
Lys Thr Pro Gln Ala Tyr Met Cys Leu Pro Arg Leu Pro Val Gly Ser		
305	310	315
Leu Val		

## (2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1083 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CWAAAACATG AGACCWRGGC WCAGACCTTA CTGTATGAGA AGCAATGCTC CTCAAACCTT	60
CTGCGTGCTG ACATAGACCT TCCCARAAGC WAAACTGTTG GCGGCGACCT GAGCGCTGGA	120
AGCCGAAGGG GAAGAGGAGG GAGACGCGAA GCCAGGGCGG YCGGCACWWA GGCGGCGGAC	180
TCGCGGSGGC AGCGCCTGCC CGGCCGGGAG CACMACCCAC GGCCCTACTC CAGCGAAGTC	240
CCGCWCCGGC TTCTAGGRAT AAAGTTACG TTYTCCTGAG GCCGCACCCC CCACYTCCCA	300
CCCAGGACGG CACATCTCCG TGTCYTCTC CCCCAAAYTC CAYTMGGGAC CCCGAGAACCC	360

AGATGTTTT AATTAAACTT TTYTCTTCCT TTTTTTTCA CTAAAGCATG TTTATTCCCC	1560
TAATCCATTA AAGAGCATGA AAAAAAGAAT AAATGTATTT GAAAATTAAA AAAAAAAA	1620
AAAAAA	1626

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 322 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Lys Thr Leu Ala Gly Leu Val Leu Gly Leu Val Ile Phe Asp Ala			
1	5	10	15
Ala Val Thr Ala Pro Thr Leu Glu Ser Ile Asn Tyr Asp Ser Glu Thr			
20	25	30	
Tyr Asp Ala Thr Leu Glu Asp Leu Asp Asn Leu Tyr Asn Tyr Glu Asn			
35	40	45	
Ile Pro Val Asp Lys Val Glu Ile Glu Ile Ala Thr Val Met Pro Ser			
50	55	60	
Gly Asn Arg Glu Leu Leu Thr Pro Pro Pro Gln Pro Glu Lys Ala Gln			
65	70	75	80
Glu Glu Glu Glu Glu Ser Thr Pro Arg Leu Ile Asp Gly Ser			
85	90	95	
Ser Pro Gln Glu Pro Glu Phe Thr Gly Val Leu Gly Pro His Thr Asn			
100	105	110	
Glu Asp Phe Pro Thr Cys Leu Leu Cys Thr Cys Ile Ser Thr Thr Val			
115	120	125	
Tyr Cys Asp Asp His Glu Leu Asp Ala Ile Pro Pro Leu Pro Lys Asn			
130	135	140	
Thr Ala Tyr Phe Tyr Ser Arg Phe Asn Arg Ile Lys Lys Ile Asn Lys			
145	150	155	160
Asn Asp Phe Ala Ser Leu Ser Asp Leu Lys Arg Ile Asp Leu Thr Ser			
165	170	175	
Asn Leu Ile Ser Glu Ile Asp Glu Asp Ala Phe Arg Lys Leu Pro Gln			

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGGGCCAGGT	TTTCCGGGCC	NTCACATTGC	CAAAAGACGG	CAATATGGTG	GGAAATAACA	60
TATAGACAAA	CGCACACCGG	CCTTATTCCA	AGCGGNTTCG	GCCAGTAACG	TTAGAATTGC	120
GGCCGCAGGT	YTAGGTCAGA	GCCAAAGGAA	AGCTTGAAAA	ATGAAGACAT	TAGCAGGACT	180
TGTTCTGGGA	CTTGTCACT	TTGATGCTGC	TGTGACTGCC	CCAACTCTAG	AGTCCATCAA	240
CTATGACTCA	GAAACCTATG	ATGCCACCTT	AGAAGACCTG	GATAATTGT	ACAACTATGA	300
AAACATACCT	GTTGATAAAAG	TTGAGATTGA	AATAGCCACA	GTGATGCCCT	CAGGGAACAG	360
AGAGCTCCTC	ACTCCACCCC	CACAGCCTGA	GAAGGCCAG	GAAGAGGAAG	AGGAGGAGGA	420
ATCTACTCCC	AGGCTGATTG	ATGGCTCTTC	TCCCCAGGAG	CCTGAATTCA	CAGGGGTTCT	480
GGGGCCACAC	ACAAATGAAG	ACTTTCCAAC	CTGTCTTTG	TGTACTTGTA	TAAGTACCAAC	540
CGTGTACTGT	GATGACCATG	AACTTGATGC	TATTCCTCCG	CTGCCAAAGA	ACACCGCTTA	600
TTTCTATTCC	CGCTTTAAC	GAATTAAAAA	GATCAACAAA	AATGACTTTG	CAAGCCTAAG	660
TGATTTAAA	AGGATTGATC	TGACATCAAA	TTTAATATCT	GAGATTGATG	AAGATGCATT	720
CCGAAAAC	CCTCAACTTC	GAGAGCTTGT	CCTGCGTGAC	AACAAAATAA	GGCAGCTCCC	780
AGAATTGCCA	ACCACTTTGA	CATTTATTGA	TATTAGCAAC	AATAGACTTG	GAAGGAAAGG	840
GATAAAGCAA	GAAGCATT	AAGACATGTA	TGATCTCCAT	CATCTGTACC	TCACTGATAA	900
CAACTTGGAC	CACATCCCTC	TGCCACTCCC	AGAAAATCTA	CGAGCCCTTC	ACCTCCAGAA	960
TAACAACATT	CTGGAAATGC	ACGAAGATAC	GTTCTGCAAT	GTTAAAATT	TGACTTATAT	1020
TCGTAAGGCA	CTAGAGGACA	TTCGATTGGA	TGGAAACCCCT	ATTAATCTCA	GCAAAACTCC	1080
TCAAGCATA	ATGTGTCTAC	CTCGTCTGCC	TGTTGGGAGC	CTTGTCTAAT	TTCAAGATAAT	1140
GGTTAGCATT	ACGATGGCTA	CTATAAATAA	ACCATTTCTTA	CTGCTCTCTT	CCAAAACAAA	1200
ACTCAGCATG	ATACTTGAG	ATTGTGTTCT	GAGAGATGAT	ATGACTACAT	AAAATACAAT	1260
TAAAAATGTT	ATAATATAAT	GAAAATGTAG	TAATTAAAGA	AAACACCAGA	TGAGTTAGGA	1320
ATAAAACCTAT	AACATTACA	AAAAGAGCAA	AYTAAGTGA	TAGAAAATAT	TTCACACATG	1380
TTCTTATAGA	TCATGTATCA	CTTGCAAGTT	TTAGGAGTTC	ATATCCTATA	TCATTTCAAA	1440
TTAAGTACAT	AATAAAGTAA	AATTTGAAA	TGAACACTTT	AGGTATTTTT	GCCAAGATT	1500

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ser Ala Gln Cys Cys Ala Gly His Leu Ala Cys Cys Cys Gly Ser  
1 5 10 15

Ala Gly Cys Ser Leu Cys Cys Asp Cys Cys Pro Arg Ile Arg Gln Ser  
20 25 30

Leu Ser Thr Arg Phe Met Tyr Ala Leu Tyr Phe Ile Leu Val Val Val  
35 40 45

Leu Cys Cys Ile Met Met Ser Thr Thr Val Ala His Lys Met Lys Glu  
50 55 60

His Ile Pro Phe Phe Glu Asp Met Cys Lys Gly Ile Lys Ala Gly Asp  
65 70 75 80

Thr Cys Glu Lys Leu Val Gly Tyr Ser Ala Val Tyr Arg Val Cys Phe  
85 90 95

Gly Met Ala Cys Phe Phe Ile Phe Cys Leu Leu Thr Leu Lys Ile  
100 105 110

Asn Asn Ser Lys Ser Cys Arg Ala His Ile His Asn Gly Phe Trp Phe  
115 120 125

Phe Lys Leu Leu Leu Gly Ala Met Cys Ser Gly Ala Phe Phe Ile  
130 135 140

Pro Asp Gln Asp Thr Phe Leu Asn Ala Trp Arg Tyr Val Gly Ala Val  
145 150 155 160

Gly Gly Phe Leu Phe Ile Gly Ile Gln Ser Ser Cys Ser Trp Ser Leu  
165 170 175

His Ile Ser Gly Thr Arg Thr Gly Val Cys Leu Tyr Gly Lys Leu Pro  
180 185 190

Ile Asp Ser Gln Lys Leu Pro Ser Phe Asp Gln Gly Cys Thr Gln Leu  
195 200 205

His Cys  
210

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1626 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CTTCGTTCAA GTGTGAGCTG CGGCTGAGCC CAGCGCTCGA GGCGCGAGGC AGCCAGGAGG	60
GCCCCGTGCAGG CGCGGGGGAGC CAGCGAGCGC GCCTTCGGCA TTGGCCGCCG CGATGTCAGC	120
TCAGTGCTGT GCGGGCCACC TGGCCTGCTG CTGTGGGTCT GCAGGCTGCT CTCTCTGCTG	180
TGATTGCTGC CCCAGGATTG GGCAGTCCT CAGCACCCGC TTCATGTACG CCCTCTACTT	240
CATTCTGGTC GTCGTCCTCT GCTGCATCAT GATGTCAACA ACCGTGGCTC ACAAGATGAA	300
AGAGCACATT CCTTTTTTG AAGATATGTG TAAAGGCATT AAAGCTGGTG ACACCTGTGA	360
GAAGCTGGTG GGATATTCTG CCGTGTATAG AGTCTGTTT GGAATGGCTT GTTTCTTCTT	420
TATCTTCTGT CTACTGACCT TGAAAATCAA CAACAGCAAA AGTTGTAGAG CTCATATTCA	480
CAATGGCTTT TGGTTCTTTA AACTTCTGCT GTGGGGGCC ATGTGCTCAG GAGCTTTCTT	540
CATTCCAGAT CAGGACACCT TTCTGAACGC CTGGCGCTAT GTGGGAGCCG TCGGAGGCTT	600
CCTCTTCATT GGCATCCAGT CCTCCTGCTC GTGGAGTTG CACATAAGTG GAACAAGAAC	660
TGGTGTGTGC CTTTATGGAA AGCTTCCCAT TGACTCACAG AAACCTGCCA GTTTGACCA	720
AGGCTGTACT CAACTGCATT GCTAGGGATT TGCAGTTTG TTTCCCTTTA TACCTGCTTT	780
TTTGTACCTC TTCATATACT CCTCTCCTTC ATTCACTTCT CACTTTTGA CCCCCCTGCC	840
CTACTCCCTT GCTTGGGCTC TGAGTCAACC AGTGGTGTGA ATTAGCCACA CTCAATCCCC	900
TGCTCGTACG GGTCTCGATC TCCTGACCTC GTGATCCGCC CACCTCGGCC TCCCAAAGTG	960
CTGGGATTAC AGGCTCGAGC CACCGCACCT GGCGTGATGD TTCTGAAAAA AAAAAAAA	1020
AAAAAAAAAA AA	1032

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 210 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth  
McCoy, John M.  
LaVallie, Edward R.  
Racie, Lisa A.  
Merberg, David  
Treacy, Maurice  
Evans, Cheryl  
Spaulding, Vikki  
Bowman, Michael  
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES  
ENCODING THEM

(iii) NUMBER OF SEQUENCES: 41

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Genetics Institute, Inc.  
(B) STREET: 87 CambridgePark Drive  
(C) CITY: Cambridge  
(D) STATE: MA  
(E) COUNTRY: U.S.A.  
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Sprunger, Suzanne A.  
(B) REGISTRATION NUMBER: 41,323

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (617) 498-8284  
(B) TELEFAX: (617) 876-5851

## (2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1032 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double

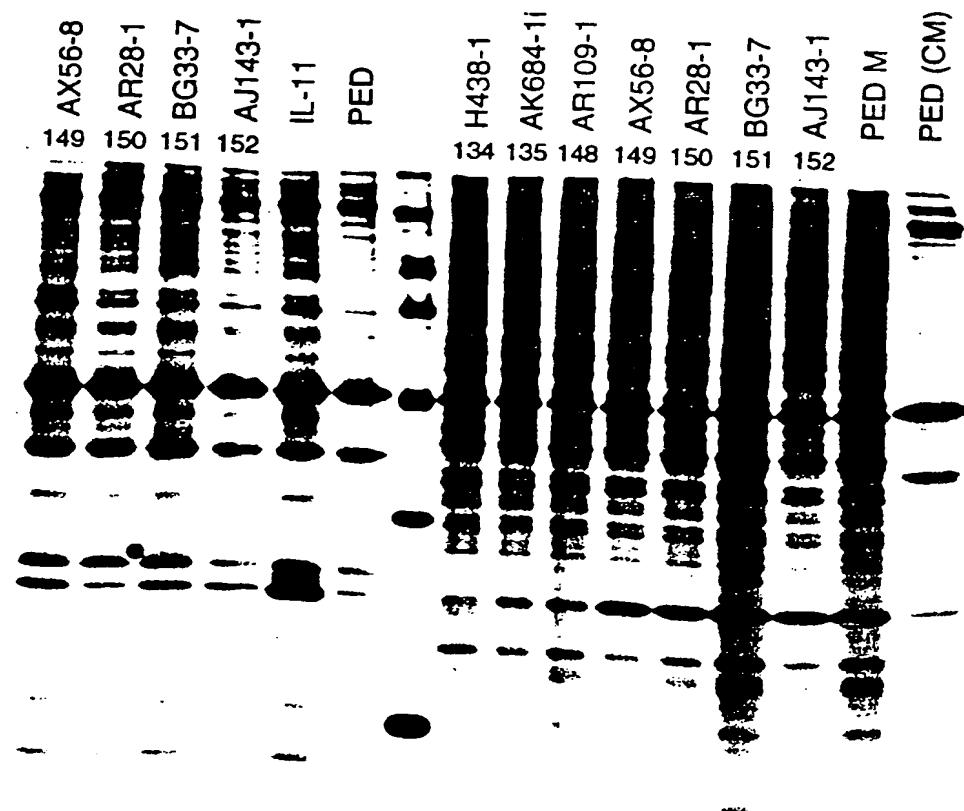


FIGURE 2

FIGURE 1B

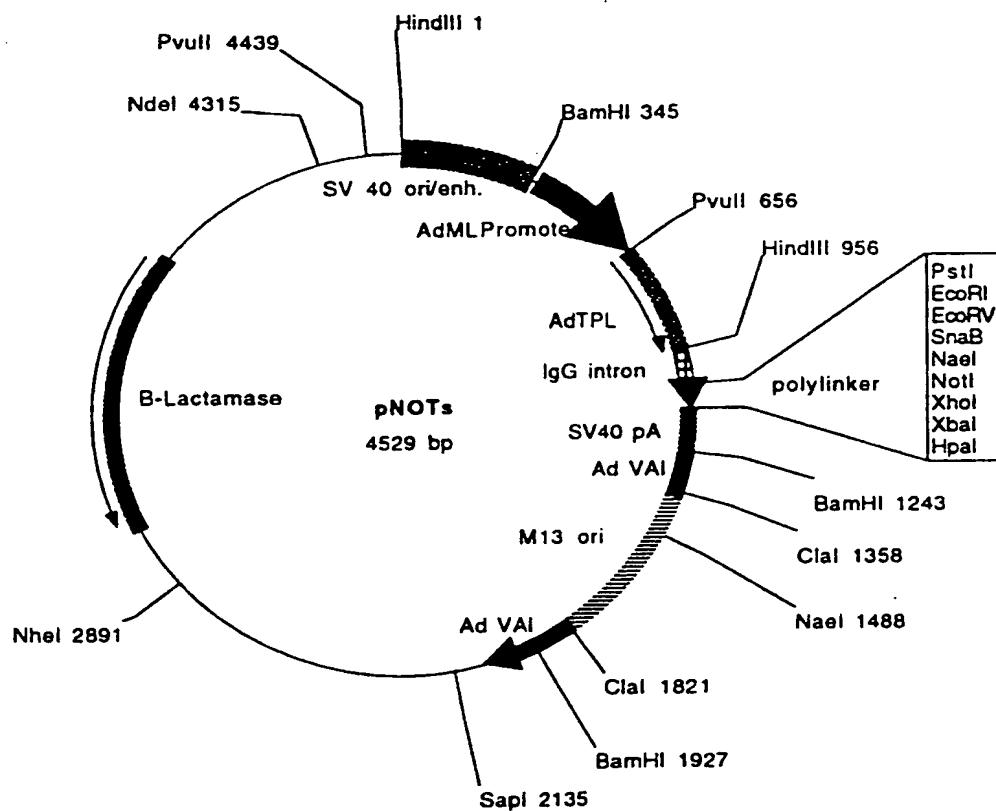
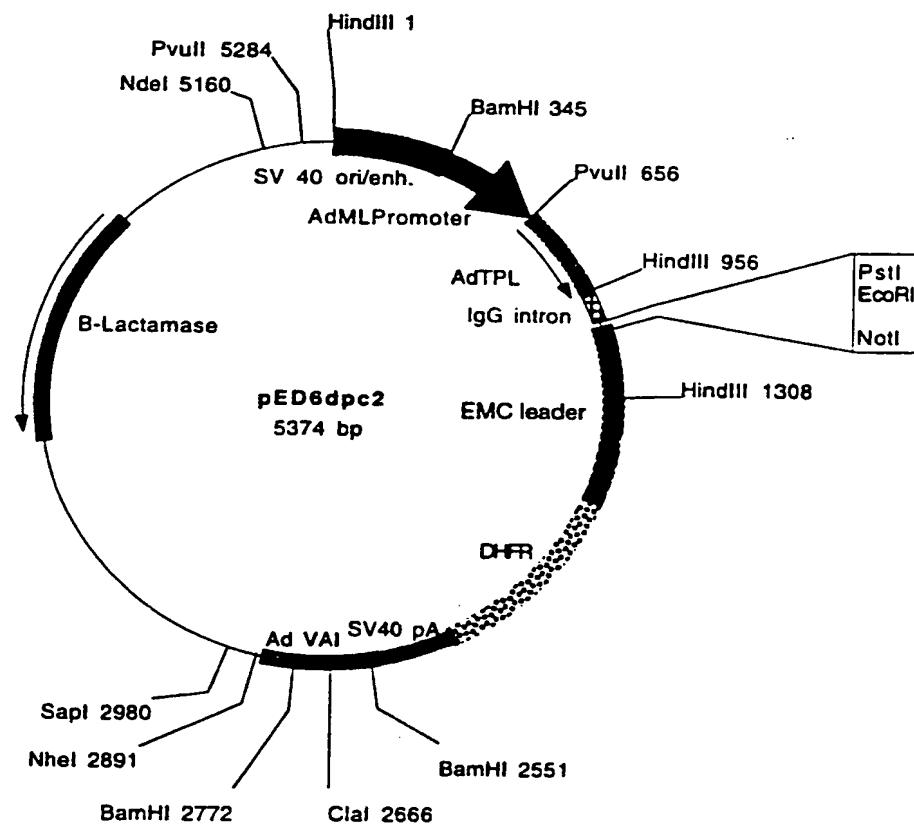


FIGURE 1A



**Plasmid name:** pED6dpc2

**Plasmid size:** 5374 bp

**Comments/References:** pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

48. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:28;
- (b) fragments of the amino acid sequence of SEQ ID NO:28; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

O289\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

49. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:27.

46. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:25.

47. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

NO:25 from nucleotide 812 to nucleotide 886;

- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:26;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:26 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

45. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:26;
- (b) fragments of the amino acid sequence of SEQ ID NO:26; and
- (c) the amino acid sequence encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

42. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:24;
- (b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112;
- (c) fragments of the amino acid sequence of SEQ ID NO:24; and
- (d) the amino acid sequence encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

the protein being substantially free from other mammalian proteins.

43. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:23.

44. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

(a) the amino acid sequence of SEQ ID NO:22;  
(b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121;  
(c) fragments of the amino acid sequence of SEQ ID NO:22; and  
(d) the amino acid sequence encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101;  
the protein being substantially free from other mammalian proteins.

40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:21.

41. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

38. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

length protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:18, SEQ ID NO:17 or SEQ ID NO:20 .

- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) fragments of the amino acid sequence of SEQ ID NO:16; and
- (c) the amino acid sequence encoded by the cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350;
- (d) a polynucleotide comprising the nucleotide sequence of the full-

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14;
- (b) fragments of the amino acid sequence of SEQ ID NO:14; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

AX56\_28 deposited under accession number ATCC 98180;

the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 51 to nucleotide 1319;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 126 to nucleotide 1319;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 409 to nucleotide 495;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX92\_3 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX92\_3 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101;

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:12;
- (b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125;
- (c) fragments of the amino acid sequence of SEQ ID NO:12; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone

AK684\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101;

(a) the amino acid sequence of SEQ ID NO:8;  
(b) fragments of the amino acid sequence of SEQ ID NO:8; and  
(c) the amino acid sequence encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101; the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 323;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
- (i) a polynucleotide encoding a protein comprising a fragment of the

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

CTCTCCTCTG GCTACTGGGT GCTCGTGGTG CATTAACTC GGAGAGAGGC CATCAAGCAG	60
ATCGAGGTGC TGCAGCACGT GGCCACCAAC CTGGGGCGCA GCCGTGCCTG GCTGTACCTG	120
GCCCTCAACG ARAACTCCCT TGGARARACT ACCTGCGGTT GTTCCARGAR AAACCTGGGC	180
CTGCTGCATA AGTACTACGT CAAGAATGCC CTGGTCTGCA GCCACGATCA CCTGACGCTC	240
TTCCTGACCT TGGTGTCCGG GCTAGAGTTG ATTCGTTTCG AGCTGGATCT GGATGCCCT	300
TACCTAGACC TGGCCCCCTA CATGCCGAC TACTACAAAC CTCAGTACCT GCTGGACTTT	360
GAAGACCGCC TTCCCAGCTC GGTCCACGGC TCAGACAGTC TGTCCCTCAA CTCTTCAAC	420
TCCGTCACCT CCACCAACCT GGAGTGGGAT GACAGTGCAG TTGCCCATC TAGTGAGGAT	480
TATGATTTG GAGATGTGTT TCCAGCAGTG CCGTCTGTAC CCAGCACAGA CTGGGAAGAT	540
GGAGACCTCA CAGACACGGT CAGTGGTCCC CGCTCCACAG CCTCCGACCT GACCAGCAGC	600
AAGGCCTCCA CCAGGAGCCC CACCCAGCGC CAGAACCCCT TCAACGAGGA GCCGGCAGAG	660
ACTGTGTCCCT CCTCTGACAC CACCCCCGTG CACACCACCT CTCAGGAGAA GGAGGAGGCC	720
CAGGCCCTGG ACCCGCCGGA TGCCTGCACG GAGCTCGAGG TCATCAGGGT CACCAAAAAA	780
<b>AAAAAAAAA</b>	789

## (2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 151 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Pro Asp Tyr Tyr Lys Pro Gln Tyr Leu Leu Asp Phe Glu Asp Arg			
1	5	10	15
Leu Pro Ser Ser Val His Gly Ser Asp Ser Leu Ser Leu Asn Ser Phe			
20	25	30	
Asn Ser Val Thr Ser Thr Asn Leu Glu Trp Asp Asp Ser Ala Ile Ala			
35	40	45	
Pro Ser Ser Glu Asp Tyr Asp Phe Gly Asp Val Phe Pro Ala Val Pro			
50	55	60	

Ser Val Pro Ser Thr Asp Trp Glu Asp Gly Asp Leu Thr Asp Thr Val  
 65 70 75 80  
 Ser Gly Pro Arg Ser Thr Ala Ser Asp Leu Thr Ser Ser Lys Ala Ser  
 85 90 95  
 Thr Arg Ser Pro Thr Gln Arg Gln Asn Pro Phe Asn Glu Glu Pro Ala  
 100 105 110  
 Glu Thr Val Ser Ser Ser Asp Thr Thr Pro Val His Thr Thr Ser Gln  
 115 120 125  
 Glu Lys Glu Glu Ala Gln Ala Leu Asp Pro Pro Asp Ala Cys Thr Glu  
 130 135 140  
 Leu Glu Val Ile Arg Val Thr  
 145 150

## (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 3443 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

AGAGACCCAA AGCCAAA ACT CAGCTGACAG GAATGTTCA AAGGACACAA AGAGAGATGT	60
GGACTCAAAG TCACCGGGGA TGCCTTATT TGAAGCAGAG GAAGGAGTTC TATCACGAAC	120
CCAGATATT CCTACCACTA TTAAAGTCAT TGATCCAGAA TTTCTGGAGG AGCCACCTGC	180
ACTTGCATT TTATATAAGG ATCTGTATGA AGAACAGTT GGAGAGAAAA AGAAGGAAGA	240
GGAGACAGCT TCTGAAGGTG ACAGTGTGAA TTCTGAGGCA TCATTTCCA GCAGAAATT	300
TGACACTGAT GATGGAACAG GAATATATT TGAGAAGTAC ATACTCAAAG ATGACATTCT	360
CCATGACACA TCTCTAACTC AAAAGGACCA GGGCCAAGGT CTGGAARAAA AACRAGTTGG	420
TAAGGATGAT TCATACCAAC CGATAGCTGC AGAAGGGAA ATTTGGGAA AGTTTGGAAC	480
TATTTGCAGG GAGAAGAGTC TGGAAGAAC AAAAGGTGTT TATGGGGAAAG GAGAATCAGT	540
AGACCATGTG GAGACCGTTG GTAACGTAGC GATGCAGAAG AAAGCTCCA TCACAGAGGA	600
CGTCAGAGTG GCTACCCAGA AAATAAGTTA TGCGGTTCCA TTTGAAGACA CCCATCATGT	660

TCTGGAGCGT GCAGATGAAG CAGGCAGTCA GGGTAATGAA GTCGGAAATG CAAGTCCAGA	720
GGTCAATCTG AATGTCCCAG TACAAGTGTG CTTCCCGGAG GAAGAATTG CATCTGGTGC	780
AACTCATGTT CAAGAACAT CACTAGAAGA ACCTAAAATC CTGGTCCCAC CTGAGCCAAG	840
TGAAGAGAGG CTCCGTAATA GCCCTGTTCA GGATGAGTAT GAATTTACAG AATCCCTGCA	900
TAATGAAGTG GTTCCTCAAG ACATATTATC AGAAGAACTG TCTTCAGAAT CCACACCTGA	960
AGATGTCTTA TCTCAAGGAA AGGAATCCTT TGAGCACATC AGTGAAAATG AATTTGCGAG	1020
TGAGGCAGAA CAAAGTACAC CTGCTGAACA AAAAGAGTTG GGCAGCGAGA GGAAAGAAGA	1080
AGACCAATTAA TCATCTGAGG TAGTAACTGA AAAGGCACAA AAAGAGCTGA AAAAGTCCCA	1140
GATTGACACA TACTGTTACA CCTGCAAATG TCCAATTCT GCCACTGACA AGGTGTTGG	1200
CACCCACAAA GACCAGAAG TTTCAACGCT TGACACAGCT ATAAGTGTG TAAAGGTTCA	1260
ATTAGCAGAA TTTCTAGAAA ATTTACAAGA AAAGTCCTTG AGGATTGAAG CCTTTGTTAG	1320
TGAGATAGAA TCCTTTTTA ATACCATTGA GGAAAAGTGT AGTAAAATG AGAAAAGGCT	1380
AGAAGAACAG AATGAGGAAA TGATGAAGAA GGTTTTAGCA CAGTATGATG AGAAAGCCCA	1440
GAGCTTGAG GAAGTGAAGA AGAAGAAGAT GGAGTTCCCTG CATGAGCAGA TGGTCCACTT	1500
TCTGCAGAGC ATGGACACTG CCAAAGACAC CCTGGAGACC ATCGTGAGAG AACGAGAGGA	1560
GCTTGATGAG GCCGTCTTCC TGACTTCGTT TGAGGAAATC AATGAAAGGT TGCTTCTGC	1620
AATGGAGAGC ACTGCTTCTT TAGAGAAAAT GCCTGCTGCG TTTTCCCTTT TTGAACATTA	1680
TGATGACAGC TCGGCAAGAA GTGACCAGAT GTTAAAACAA GTGGCTGTT CACAGCTTCC	1740
TAGATTAGAA CTCAGGAACC AAATTTGCC ACCAGCACAA CAATTGCAGT TTACTGGAGC	1800
ATGAACAAGG AAGATGTCAT TGATTCAATT CAGGTTACT GCATGGAGGA GCCACAAGAT	1860
GATCAAGAAC TAAATGAGTT GGTAGAAGAA TACAGACTGA CAGTGAAGA AAGCTACTGC	1920
ATTTTGAAAG ATCTGGAACC TGACCGATGC TATCAAGTGT GGGTGATGGC TGTGAACCTTC	1980
ACTGGATGTA GCCTGCCAG TGAAAGGGCC ATTTTAGGA CAGCACCCCTC CACCCCTGTG	2040
ATCCGCGCTG AGGACTGTAC TGTGTGTTGG AACACAGCCA CTATCCGATG GCGGCCACC	2100
ACCCCCAGAGG CCACGGAGAC CTACACTCTG GAGTACTGCA GACAGCACTC TCCTGAGGGA	2160
GAGGGCCTCA GATCTTCTC TGGAATCAAA GGACTCCAGC TGAAAGTTAA CCTCCAACCC	2220
AATGATAACT ACTTTTTTA TGTGAGGGCC ATCAATGCAT TTGGGACAAG TGAACAGAGT	2280
GAAGCTGCTT TCATCTCCAC CAGAGGAACC AGATTTCTCT TGTTGAGAGA AACAGCTCAT	2340

CCTGCTCTAC ACATTCCTC AAGTGGGACA GTGATCAGCT TTGGTGAGAG GAGACGGCTG	2400
ACGGAAATCC CGTCAGTGCT GGGTGAGGAG CTGCCTTCCT GTGCCAGCA TTACTGGAA	2460
ACCACAGTCA CAGACTGCCC AGCATATCGA CTCGGCATCT GCTCCAGCTC GGCTGTGCAG	2520
GCAGGTGCC TAGGACAAGG GGAGACCTCA TGGTACATGC ACTGCTCTGA GCCACAGAGA	2580
TACACATTT TCTACAGTGG TATTGTGAGT GATGTTCATG TGACTGAGCG TCCAGCCAGA	2640
GTGGGCATCC TGCTGGACTA CAACAACCAG AGATTATCTT CATCAACGCA GAGAGCGAGC	2700
AGTTGCTCTT CATCATCAGG CACAGGTTA ATGAGGGTGT CCACCCTGCC TTTGCCCTGG	2760
AGAAACCTGG AAAATGTACT TTGCACCTGG GGATAGAGCC CCCGGATTCT GTAAGGCACA	2820
AGTGATCCTT GGCTTCAGA ATTTGCAAGA ACAGCGATTG GAATTTGGG GGGGTCTGCT	2880
GTTCATTCCT TTAGGTGCTA TACATTATTC AAAAAGTCTC CCGCGCATTG GCACTAATGA	2940
TGGCTGCATG CATAGCAATC AGCATGTGAG CAAATCGAC AAGAAAACCT TGACTTTACA	3000
GAGCAGTGTG TGAGTAAACA GAATGAAAAC AACAACCTCC ACTCTTAGT TTATATAAGT	3060
TTGAGTTCTT TCCTAAATTA AAAGATCTAC ACTTGAGTTG GGAACCGAAA GAGAAAATG	3120
GACTTCCATC TGTTTACTG GTAAAGGAAA TCCTCTGATG GACAGGTCAG AGTGAAGGAA	3180
GGTTGTGCTG GTAAGACATC TCTGACGAAG AGCCATGGAT GCTTCCACA AAATGTCACC	3240
TCGCTGCACT AAAGGATGAT GAATCCTAAT CATTAAAGGA ATTGTTTCAG CTGATTTAAA	3300
TTTATAATGA ACTCTTTGT AATAATGTAT ACTGTAGAAC ATGAGTCTCT CCTCCCTAAA	3360
ATTTTAAATG TAGAAAAGTG CTATATATTA GAAATTCCA TTTTGTAAA TAAATGGTTA	3420
GAGTCTATAA AAAAAAAA AAA	3443

## (2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 574 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met	Pro	Leu	Phe	Glu	Ala	Glu	Gly	Val	Leu	Ser	Arg	Thr	Gln	Ile
1									5					10
														15

Phe	Pro	Thr	Thr	Ile	Lys	Val	Ile	Asp	Pro	Glu	Phe	Leu	Glu	Glu	Pro
20															30
Pro	Ala	Leu	Ala	Phe	Leu	Tyr	Lys	Asp	Leu	Tyr	Glu	Glu	Ala	Val	Gly
35															45
Glu	Lys	Lys	Glu	Glu	Glu	Thr	Ala	Ser	Glu	Gly	Asp	Ser	Val	Asn	
50															60
Ser	Glu	Ala	Ser	Phe	Pro	Ser	Arg	Asn	Ser	Asp	Thr	Asp	Asp	Gly	Thr
65															80
Gly	Ile	Tyr	Phe	Glu	Lys	Tyr	Ile	Leu	Lys	Asp	Asp	Ile	Leu	His	Asp
85															95
Thr	Ser	Leu	Thr	Gln	Lys	Asp	Gln	Gly	Gln	Gly	Leu	Glu	Xaa	Lys	Xaa
100															110
Val	Gly	Lys	Asp	Asp	Ser	Tyr	Gln	Pro	Ile	Ala	Ala	Glu	Gly	Glu	Ile
115															125
Trp	Gly	Lys	Phe	Gly	Thr	Ile	Cys	Arg	Glu	Lys	Ser	Leu	Glu	Glu	Gln
130															140
Lys	Gly	Val	Tyr	Gly	Glu	Gly	Glu	Ser	Val	Asp	His	Val	Glu	Thr	Val
145															160
Gly	Asn	Val	Ala	Met	Gln	Lys	Lys	Ala	Pro	Ile	Thr	Glu	Asp	Val	Arg
165															175
Val	Ala	Thr	Gln	Lys	Ile	Ser	Tyr	Ala	Val	Pro	Phe	Glu	Asp	Thr	His
180															190
His	Val	Leu	Glu	Arg	Ala	Asp	Glu	Ala	Gly	Ser	Gln	Gly	Asn	Glu	Val
195															205
Gly	Asn	Ala	Ser	Pro	Glu	Val	Asn	Leu	Asn	Val	Pro	Val	Gln	Val	Ser
210															220
Phe	Pro	Glu	Glu	Glu	Phe	Ala	Ser	Gly	Ala	Thr	His	Val	Gln	Glu	Thr
225															240
Ser	Leu	Glu	Glu	Pro	Lys	Ile	Leu	Val	Pro	Pro	Glu	Pro	Ser	Glu	Glu
245															255
Arg	Leu	Arg	Asn	Ser	Pro	Val	Gln	Asp	Glu	Tyr	Glu	Phe	Thr	Glu	Ser
260															270
Leu	His	Asn	Glu	Val	Val	Pro	Gln	Asp	Ile	Leu	Ser	Glu	Glu	Leu	Ser
275															285
Ser	Glu	Ser	Thr	Pro	Glu	Asp	Val	Leu	Ser	Gln	Gly	Lys	Glu	Ser	Phe
290															300
Glu	His	Ile	Ser	Glu	Asn	Glu	Phe	Ala	Ser	Glu	Ala	Glu	Gln	Ser	Thr

305	310	315	320
Pro Ala Glu Gln Lys Glu Leu Gly Ser Glu Arg Lys Glu Glu Asp Gln			
325	330	335	
Leu Ser Ser Glu Val Val Thr Glu Lys Ala Gln Lys Glu Leu Lys Lys			
340	345	350	
Ser Gln Ile Asp Thr Tyr Cys Tyr Thr Cys Lys Cys Pro Ile Ser Ala			
355	360	365	
Thr Asp Lys Val Phe Gly Thr His Lys Asp His Glu Val Ser Thr Leu			
370	375	380	
Asp Thr Ala Ile Ser Ala Val Lys Val Gln Leu Ala Glu Phe Leu Glu			
385	390	395	400
Asn Leu Gln Glu Lys Ser Leu Arg Ile Glu Ala Phe Val Ser Glu Ile			
405	410	415	
Glu Ser Phe Phe Asn Thr Ile Glu Glu Asn Cys Ser Lys Asn Glu Lys			
420	425	430	
Arg Leu Glu Glu Gln Asn Glu Glu Met Met Lys Lys Val Leu Ala Gln			
435	440	445	
Tyr Asp Glu Lys Ala Gln Ser Phe Glu Glu Val Lys Lys Lys Lys Met			
450	455	460	
Glu Phe Leu His Glu Gln Met Val His Phe Leu Gln Ser Met Asp Thr			
465	470	475	480
Ala Lys Asp Thr Leu Glu Thr Ile Val Arg Glu Ala Glu Glu Leu Asp			
485	490	495	
Glu Ala Val Phe Leu Thr Ser Phe Glu Glu Ile Asn Glu Arg Leu Leu			
500	505	510	
Ser Ala Met Glu Ser Thr Ala Ser Leu Glu Lys Met Pro Ala Ala Phe			
515	520	525	
Ser Leu Phe Glu His Tyr Asp Asp Ser Ser Ala Arg Ser Asp Gln Met			
530	535	540	
Leu Lys Gln Val Ala Val Pro Gln Leu Pro Arg Leu Glu Leu Arg Asn			
545	550	555	560
Gln Ile Leu Pro Pro Ala Gln Gln Leu Gln Phe Thr Gly Ala			
565	570		

## (2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1199 base pairs
  - (B) TYPE: nucleic acid

(C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

RGACTTGTG	CCAGTGATAC	CAAAACAGAC	TTTCCCAAG	CAGTGCCTCA	CATGTCTGCT	60
GGTGTGGCTT	TGGGATTCTC	CTGCCCCACC	CCCCCGTCCA	TGGCAGCCCC	CTCCCCAAGG	120
CTTGCTCAC	ACCTGAGACA	GGAAGGAGGA	AGGGGATCCA	ATAGGAATAT	GGGCCCCGGA	180
GGGGAAGTCA	TGCACCCCCA	AGCCACCACC	CCCCAGCCTT	CCACGCACAT	CTCCTGGYTG	240
GAAGAGAGCC	CTCCAAAAAG	GGGACACAGG	CTGCCCCGGC	CCCTCAACTG	CATCCACACC	300
CCATCCTCTC	ATCTTGGTC	CCAGCCAGGC	CCCCCCAAAA	CCAAAGCCCC	CTCAAGTCCT	360
GGGGTCCCAG	CCTGTGCCCC	CAGCTTCCTG	CCCACCCAGC	CCTGAGCATT	CTCACACAGA	420
GAAAGAACAA	GCAAGGGCTC	CAGGGGGACA	GGATGGGGCA	GGGCATACAG	TGGGGGGTGG	480
GGGGCAGCT	GGGAGGGAGG	AGGGACAAAA	CAAAACATT	TCCTTGGGT	TTTTTTTTTC	540
TTTCTTTTT	CTCCCCTTA	CTCTTGGGT	GGTGTGCTT	TTCTTTCCT	TTTCCCTTTG	600
AGATTTTTT	GTTGTTGTTT	CCTTTTGTA	TTTACTGAT	ATCACCAGGA	TAGTTTACTC	660
TCCTCTAGC	TTCTGCTTA	CCGCACACTG	GATAACACAC	ACATACACAC	CCACAAAAAT	720
GCTCATGAAC	CCAATCCGGA	GAAGGTTCCA	GCAGGTCCCC	CACCCCTCCC	TCCTCCTCCT	780
ACTTCTCCTC	TTGACAGCGA	GGACAGGAGG	GGGACAAGGG	GACACCTGGG	CAGACCCGCC	840
GGCTCTCCCC	CCACCCACC	CCGCCCCCTCA	CATCATACTC	CAATCATAAC	CTTGTATATT	900
ACGCAGTCAT	TTGGTTTTC	CGGGACGCGC	CTACCTAAGT	ACCATTACA	GAAAGTGACT	960
CTGGCTGTCA	TTATTTGTT	TATTTGTTCC	CTATGAAAAA	AAAAAATGAA	AATGAAAAAA	1020
GGGGGATTCC	ATAAAAGATT	CAATAAAAGA	CAAACAAAAA	AAAAAGAAAA	AAGAAAAAAA	1080
TGTATAAAAA	TTAAACAAGC	TATGCTTCGA	CTCAAAAAAA	AAAAAAA	AAAAAAA	1140
AAAAAAA	AAAAAAA	AAAAAAA	AAAAAAA	AAAAAAA	AAAAAAA	1199

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 56 amino acids  
 (B) TYPE: amino acid

(C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Leu Met Asn Pro Ile Arg Arg Arg Phe Gln Gln Val Pro His Pro  
 1 5 10 15

Pro Leu Leu Leu Leu Leu Leu Leu Thr Ala Arg Thr Gly Gly Gly  
 20 25 30

Gln Gly Asp Thr Trp Ala Asp Pro Pro Ala Leu Pro Pro Pro His Pro  
 35 40 45

Ala Pro His Ile Ile Leu Gln Ser  
 50 55

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 839 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GAATGAAAAT CCAGGTGTTT GTCATTACATC AGAACAGGT GATCCCCATT GCAGGCAGCC	60
GGAACCGACG TCTCCTGGAC CACTGAGCTG GCTGTTCTCA TTACTGCCCT TTCCGCCAG	120
GCTGGCGGTG ACTCACCGTG AGACAAGTCA GCTAGGTGTT CAGGACAGGG ATTCAGAGT	180
ATTTTTGTCC AAAGAGGAAA GGGATGATTT CTACGGATCA CTACCAGTTG GTTTACTGTT	240
AGCTNCATCG TGTTGATCAC ACCAAGTCCT TGCCAATTG GTTTCTAAG TATTTTCACG	300
CCTTCTCCTC GTGTCCGCGT CACTGCTCTG ATTCAAGGCC TTGTCATTTC TCATCTTGC	360
CATTTTAGTA GTTTTGGAT TGGGCTCCCG GCTGCTAATT TTGTCCCCTT TTCCACTATC	420
TTCCACATTG TCACCGCAGT CATGTTCTA AGGCAGAAC TCACTGTGCC CCTCATCGTG	480
TTGGGTGACT TSTGGTGGCA TCCCGTCACC CTCAGGACAA CCTTTCTGG GGCTGCCCG	540

CTCTGCTCTT GCTGCTGCCT CGCTGTCCCC CTCCTCCCTC CTGTGGTTA TATTCCAGGA	600
ATTCTGAATT AGTTGCACCG TGCTCTCATA TTTACTGCAA GAATAGACCA GTGGTTCTCC	660
AGCTTTCTG CACTCTGGAA TCACCTGGGG GTCTTTAAAA AACACTGCCT GGCTCCTAGT	720
CCTAAATTTG GAGATTAAAC TGGACTTACA GTTTTCAAA GCACCCAAA AGATTCTAAT	780
GTGCAGCAAA GTTTGGGAAC CACTGGTATA GACTGTCTTC TGCTTGTTT CTTGAAAAA	839

## (2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 56 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Phe Leu Arg Gln Asn Leu Thr Val Pro Leu Ile Val Leu Gly Asp			
1	5	10	15
Xaa Trp Trp His Pro Val Thr Leu Arg Thr Thr Phe Pro Gly Ala Cys			
20	25	30	
Pro Leu Cys Ser Cys Cys Cys Leu Ala Val Pro Leu Leu Pro Pro Val			
35	40	45	
Val Tyr Ile Pro Gly Ile Leu Asn			
50	55		

## (2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ANTATCCAC CAGCTTCTCA CAGGTGTCA

29

## (2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GNAGGCATCA CTGTGGCTAT TTCAATCTC

29

## (2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TNCCATCTAC CGCAACTCTC AGTCGAGA

29

## (2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TNAGTGTAGT GACAGTGGTG ACATCCTTT

29

## (2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 27 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid  
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

TGAAGGGGTC TGAAAAGGGC AGATGAG

27

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid  
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

TNTTGGTGGA GATGCCATCC GGAACCTCA

29

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid  
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GNTCTTGGGA TGCCTCGCCC TGCAGATAA

29

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid  
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GNAAGCCGAC AAGTTTCGTC TTCCTATAA

29

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid  
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GNTAAACCAA GGTGGTAGTA ATGGAGTGG

29

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid  
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GNTTGGTGGAA GGTGACGGAG TTGAAAGAG

29

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GNCTCCTCCA GAAATTCTGG ATCAATGAC

29

- (2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 27 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

TCCTCCTACT TCTCCTCTTG ACAGCGA

27

- (2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TNCCTTAGAA ACATGACTGC GGTGACAAT

29

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/22034

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 21/04; C07K 14/705; C12N 15/09, 15/63; C12Q 1/68  
US CL : 536/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, JAPIO, SCISEARCH, WPIDS, EMBASE, EMBL-EST55, EMBL55, N-GENESEQ32, N-ISSUED, PIR  
search terms: atcc 98101, ac41\_1

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	Database GENBANK on STN, National Institute of Health, Accession No. L20319, PFEIFFER, S.S. Rattus Norvegicus Developmentally Regulated Protein mRNA, Complete cds, Emb153 Database. 30 June 1993.	1 ---- 2-12
Y	WO 94/01548 A2 (MEDICAL RESEARCH COUNCIL) 20 January 1994, see entire document.	1-12

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 JANUARY 1999	Date of mailing of the international search report 01 FEB 1999
--	---

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized Officer NIRMAL S. BASI Telephone No. (703) 308-0196
---	--

**INTERNATIONAL SEARCH REPORT**

International application No. PCT/US98/22034
---

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-13

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US98/22034

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING**

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-13, drawn to clone AC41-1 encoding the protein of SEQ ID NO:2.  
Group II, claim(s)14-16, drawn to clone AC222-1 encoding the protein of SEQ ID NO:4.  
Group III, claim(s)17-19, drawn to clone AJ143-1 encoding the protein of SEQ ID NO:6.  
Group IV, claim(s)20-22, drawn to clone AC168-1 encoding the protein of SEQ ID NO:8.  
Group V, claim(s)23-25, drawn to clone AK684-1 encoding the protein of SEQ ID NO:10.  
Group VI, claim(s)26-28, drawn to clone AS209-1 encoding the protein of SEQ ID NO:12.  
Group VII, claim(s)29-31, drawn to clone AX56-28 encoding the protein of SEQ ID NO:14.  
Group VIII, claim(s)32-34, drawn to clone AX92-3 encoding the protein of SEQ ID NO:16.  
Group IX, claim(s)35-37, drawn to clone BF245-1 encoding the protein of SEQ ID NO:19.  
Group X, claim(s)38-40, drawn to clone B633-7 encoding the protein of SEQ ID NO:22.  
Group XI, claim(s)41-43, drawn to clone BM46-10 encoding the protein of SEQ ID NO:24.  
Group XII, claim(s)44-46, drawn to clone J317-1 encoding the protein of SEQ ID NO:26.  
Group XIII, claim(s)47-49, drawn to clone O289-1 encoding the protein of SEQ ID NO:28.

The inventions listed as Groups I-XIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is directed to polynucleotide and polypeptide disclosed in SEQ ID NO:1 and SEQ ID NO:2 and present in clone AC41-1, allelic variants, polynucleotides capable of hybridizing to said polynucleotide sequence, host cells transformed with said polynucleotide, isolated gene containing said polynucleotide and method for preventing, treating or ameliorating a medical condition using said polypeptide. The special technical feature of Group I is the polypeptide and polynucleotide disclosed in SEQ ID NO:1 and SEQ ID NO:2. Groups II-XIII do not share the special technical feature of Group I, instead they are directed to a other polypeptide and polynucleotides structurally different to those of Group I.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07H 21/04, C07K 14/705, C12N 15/09, 15/63, C12Q 1/68</b>		A1	(11) International Publication Number: <b>WO 99/20644</b> (43) International Publication Date: <b>29 April 1999 (29.04.99)</b>
(21) International Application Number: <b>PCT/US98/22034</b>		(74) Agent: SPRUNGER, Suzanne, A.; American Home Products Corporation, Patent & Trademark Dept. – 2B, One Campus Drive, Parsippany, NJ 07054 (US).	
(22) International Filing Date: <b>16 October 1998 (16.10.98)</b>		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: <b>08/955,557 18 October 1997 (18.10.97) US</b>		Published <i>With international search report.</i>	
(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 Cambridge Park Drive, Cambridge, MA 02140 (US).			
(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 113 Ann Lee Road, Harvard, MA 01451 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). MERRBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). EVANS, Cheryl; 111 Locust Street #41, Woburn, MA 01801 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). BOWMAN, Michael, R.; 50 Aldrich Road, Canton, MA 02021 (US). AGOSTINO, Michael, J.; 26 Wolcott Avenue, Andover, MA 01810 (US).			

(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

## (57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

5

## SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of the following applications: Ser. No. 08/677,231, filed July 9, 1996; Ser. No. 08/701,819, filed August 23, 1996; Ser. No. 08/721,488, filed September 27, 1996; and Ser. No. 08/739,066, filed October 28, 1996.

10

15

### FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

20

25

30

### BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

### SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising

an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 179 to nucleotide 742;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1

from nucleotide 179 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568; the nucleotide sequence of the full-length protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC41\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

10 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the 15 group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
- (b) the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129;
- (c) fragments of the amino acid sequence of SEQ ID NO:2; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AC41\_1 deposited under accession number ATCC 98101;

20 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

25 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:3 from nucleotide 218 to nucleotide 1126;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:3 from nucleotide 1 to nucleotide 553;

(e) a polynucleotide comprising the nucleotide sequence of the full-

5 length protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;

10 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 15 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

20 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

25 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 218 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553; the nucleotide sequence of the full-length protein coding sequence of clone AC222\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC222\_1 deposited

5

under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

10

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:4;
- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131;
- (c) fragments of the amino acid sequence of SEQ ID NO:4; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AC222\_1 deposited under accession number ATCC 98101;

15

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

20

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

25

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101;

30

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101;

5 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

10 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

15 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

20 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994; the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994; the nucleotide sequence of the full-length protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ143\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20.

25

30 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising

a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:6;
- (b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to 5 amino acid 20;
- (c) fragments of the amino acid sequence of SEQ ID NO:6; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AJ143\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such 10 protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ168\_4 deposited under accession 20 number ATCC 98101;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168\_4 deposited under accession 25 number ATCC 98101;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- 5 (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

10 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204; the nucleotide sequence of the full-length protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ168\_4 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101.

15 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:8;
- (b) 20 fragments of the amino acid sequence of SEQ ID NO:8; and
- (c) the amino acid sequence encoded by the cDNA insert of clone AJ168\_4 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8.

25 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) 30 a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:9 from nucleotide 1 to nucleotide 323;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101;

5 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101;

10 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101;

15 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

15 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

20 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 323; the nucleotide sequence of the full-length protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AK684\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the 30 polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AK684\_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) fragments of the amino acid sequence of SEQ ID NO:10; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

AK684\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101;

5 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

10 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

15 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

20 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186; the nucleotide sequence of the full-length protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AS209\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101.

25 In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

30 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125;

(c) fragments of the amino acid sequence of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS209\_1 deposited under accession number ATCC 98101; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

5 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- 10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890;
- 15 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180;
- 20 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180;
- 25 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

5 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708; the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890; the nucleotide sequence of the full-length protein coding sequence of clone AX56\_28 deposited under accession number ATCC 98180; or the nucleotide sequence of the mature protein coding sequence of clone 10 AX56\_28 deposited under accession number ATCC 98180. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AX56\_28 deposited under accession number ATCC 98180.

15 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

20 (a) the amino acid sequence of SEQ ID NO:14;

(b) fragments of the amino acid sequence of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone

AX56\_28 deposited under accession number ATCC 98180;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14.

25 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 51 to nucleotide 1319;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:15 from nucleotide 126 to nucleotide 1319;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:15 from nucleotide 409 to nucleotide 495;

(e) a polynucleotide comprising the nucleotide sequence of the full-

5 length protein coding sequence of clone AX92\_3 deposited under accession  
number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the  
cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101;

10 (g) a polynucleotide comprising the nucleotide sequence of the  
mature protein coding sequence of clone AX92\_3 deposited under accession  
number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the  
cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101;

15 (i) a polynucleotide encoding a protein comprising the amino acid  
sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the  
amino acid sequence of SEQ ID NO:16 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of  
20 (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the  
protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent  
conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID

25 NO:15 from nucleotide 51 to nucleotide 1319; the nucleotide sequence of SEQ ID

NO:15 from nucleotide 126 to nucleotide 1319; the nucleotide sequence of SEQ ID

NO:15 from nucleotide 409 to nucleotide 495; the nucleotide sequence of the full-length

protein coding sequence of clone AX92\_3 deposited under accession number ATCC

98101; or the nucleotide sequence of the mature protein coding sequence of clone

30 AX92\_3 deposited under accession number ATCC 98101. In other preferred  
embodiments, the polynucleotide encodes the full-length or mature protein encoded by

the cDNA insert of clone AX92\_3 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) fragments of the amino acid sequence of SEQ ID NO:16; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

AX92\_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid

sequence of SEQ ID NO:19;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

5 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

10 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350; the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350; the nucleotide sequence of the full-length protein coding sequence of clone BF245\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone 15 BF245\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18, SEQ ID NO:17 or SEQ ID NO:20.

20 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

25 (c) the amino acid sequence encoded by the cDNA insert of clone BF245\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:19.

30 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:21;

- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477;
- 5 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101;
- 10 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101;
- 15 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;
- 20 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- 25 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774; the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477; the nucleotide sequence of the full-length protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BG33\_7 deposited under accession number ATCC 98101. In other preferred

embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BG33\_7 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

5 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the 10 group consisting of:

- (a) the amino acid sequence of SEQ ID NO:22;
- (b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121;
- (c) fragments of the amino acid sequence of SEQ ID NO:22; and
- (d) the amino acid sequence encoded by the cDNA insert of clone

15 BG33\_7 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22 or the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

20 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152;
- (e) a polynucleotide encoding the full-length protein encoded by the

cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

5 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

10 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

15 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

20 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801; the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421; the nucleotide sequence of the full-length protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152; or the nucleotide sequence of the mature protein coding sequence of clone BM46\_10 deposited under accession number ATCC 98152. In other preferred

25 embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152.

In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112.

30 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:23.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:24;
- 5 (b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112;
- (c) fragments of the amino acid sequence of SEQ ID NO:24; and
- (d) the amino acid sequence encoded by the cDNA insert of clone BM46\_10 deposited under accession number ATCC 98152;

10 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:24 or the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 15 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886;
- 20 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101;
- 25 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101;
- 30 (h) a polynucleotide encoding the mature protein encoded by the

cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:26;

5 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:26 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

10 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853; the nucleotide sequence of the full-length protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone J317\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101.

20 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:25.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the 25 group consisting of:

(a) the amino acid sequence of SEQ ID NO:26;

(b) fragments of the amino acid sequence of SEQ ID NO:26; and

(c) the amino acid sequence encoded by the cDNA insert of clone J317\_1 deposited under accession number ATCC 98101;

30 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:26.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;
- 5 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483;
- 10 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101;
- 15 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101;
- 20 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- 25 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609; the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483; the nucleotide sequence of the full-length

protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone O289\_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone O289\_1 deposited under accession number ATCC 98101.

5 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:27.

10 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:28;
- (b) fragments of the amino acid sequence of SEQ ID NO:28; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

15 O289\_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:28.

20 In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

25 The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

30 Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically

effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

#### BRIEF DESCRIPTION OF DRAWINGS

5 Fig. 1A and Fig. 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

Fig. 2 is an autoradiograph evidencing the expression of the following clone disclosed herein, BG33\_7.

10

#### DETAILED DESCRIPTION

##### ISOLATED PROTEINS AND POLYNUCLEOTIDES

15

20

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

25

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

30

##### Clone "AC41\_1"

A polynucleotide of the present invention has been identified as clone "AC41\_1".

5

AC41\_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC41\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC41\_1 protein").

10

The nucleotide sequence of AC41\_1 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC41\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 10 to 22 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 23, or are a transmembrane domain.

15

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC41\_1 should be approximately 1000 bp.

20

25

The nucleotide sequence disclosed herein for AC41\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AC41\_1 demonstrated at least some homology with sequences identified as L20319 (Rattus norvegicus developmentally regulated protein mRNA, complete cds), U46493 (Cloning vector pFlp recombinase gene, complete cds), and Z22650 (H.sapiens insertion polymorphism DNA). The predicted amino acid sequence disclosed herein for AC41\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AC41\_1 protein demonstrated at least some identity with sequences identified as L20319 (developmentally regulated protein [Rattus norvegicus]) and X12544 (3 HLA-DR B protein precursor (AA -29 to 267) [Homo sapiens]). Based upon homology, AC41\_1 proteins and each homologous protein or peptide may share at least some activity.

#### Clone "AC222\_1"

30

A polynucleotide of the present invention has been identified as clone "AC222\_1". AC222\_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No.

5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC222\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC222\_1 protein").

5 The nucleotide sequence of AC222\_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC222\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Amino acids 7 to 19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at 10 amino acid 20, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC222\_1 should be approximately 1400 bp.

15 The nucleotide sequence disclosed herein for AC222\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AC222\_1 demonstrated at least some homology with sequences identified as D10485 (Chicken mRNA for proteoglycan (PG-Lb) core protein, complete cds), D78274 (Mouse mRNA for proteoglycan, complete cds), N22463 (yw34c10.s1 Homo sapiens cDNA clone 254130 3'), U59111 (Human dermatan sulfate 20 proteoglycan 3 (DSPG3) mRNA, complete cds), U77127 (Bos taurus epiphycan mRNA, complete cds), and Z32693 (E.coli pT7hGH\_pl DNA, 6160bp). The predicted amino acid sequence disclosed herein for AC222\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted 25 AC222\_1 protein demonstrated at least some identity with sequences identified as D10485 (proteoglycan core protein [Gallus gallus]), D78274 (proteoglycan [Mus musculus]), U77127 (epiphycan [Bos taurus]), and U59111 (dermatan sulfate proteoglycan 3 [Homo sapiens]). Based upon homology, AC222\_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AJ143\_1"

30 A polynucleotide of the present invention has been identified as clone "AJ143\_1". AJ143\_1 was isolated from a human adult testes cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ143\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ143\_1 protein").

5 The nucleotide sequence of AJ143\_1 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AJ143\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 2 to 14 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at 10 amino acid 15, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ143\_1 should be approximately 1000 bp.

15 The nucleotide sequence disclosed herein for AJ143\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ143\_1 demonstrated at least some homology with sequences identified as T19431 (d08002s Homo sapiens cDNA clone d08002 5' end) and Z41997 (H. sapiens partial cDNA sequence; clone c-05c07); it may also show some similarity to phosphoenolpyruvate phosphomutase. Based upon homology, AJ143\_1 20 proteins and each homologous protein or peptide may share at least some activity.

#### Clone "AJ168\_4"

25 A polynucleotide of the present invention has been identified as clone "AJ168\_4". AJ168\_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ168\_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ168\_4 protein").

30 The nucleotide sequence of AJ168\_4 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the AJ168\_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ168\_4 should be approximately 700 bp.

5 The nucleotide sequence disclosed herein for AJ168\_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ168\_4 demonstrated at least some homology with sequences identified as T65223 (yc79c02.s1 Homo sapiens cDNA clone 22106 3'). Based upon homology, AJ168\_4 proteins and each homologous protein or peptide may share 10 at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AJ168\_4 protein sequence (SEQ ID NO:8).

#### Clone "AK684\_1"

15 A polynucleotide of the present invention has been identified as clone "AK684\_1". AK684\_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AK684\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also 20 referred to herein as "AK684\_1 protein").

The nucleotide sequence of AK684\_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AK684\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

25 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AK684\_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AK684\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AK684\_1 demonstrated at least some homology with sequences identified as AA226405 (nc20c05.r1 NCI CGAP Pr1 Homo sapiens cDNA 30 clone 2817), G15531 (human STS SHGC-17023), and T68858 (yc30d08.s1 Homo sapiens

cDNA clone 82191 3' similar to contains MSR1 repetitive element). Based upon homology, AK684\_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AK684\_1 protein sequence centered around amino acid 20 of SEQ ID NO:10.

5

Clone "AS209\_1"

10

A polynucleotide of the present invention has been identified as clone "AS209\_1". AS209\_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AS209\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS209\_1 protein").

15

20

The nucleotide sequence of AS209\_1 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AS209\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 32 to 44 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 45, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS209\_1 should be approximately 2882 bp.

25

30

The nucleotide sequence disclosed herein for AS209\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AS209\_1 demonstrated at least some homology with sequences identified as AA055217 (zf17h02.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 377235 3') and H29533 (ym60h11.r1 Homo sapiens cDNA clone 52955 5' similar to SP:A60164 S34329; PLATELET MEMBRANE GLYCOPROTEIN V PRECURSOR). The predicted amino acid sequence disclosed herein for AS209\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AS209\_1 protein demonstrated at least some

identity with sequences identified as D63875 (ORF [Homo sapiens]) and X53959 (slit protein [Drosophila melanogaster]). Based upon homology, AS209\_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AS209\_1 protein sequence, centered around amino acids 32, 387, 449, and 538 of SEQ ID NO:12.

5

Clone "AX56\_28"

10

A polynucleotide of the present invention has been identified as clone "AX56\_28". AX56\_28 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX56\_28 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX56\_28 protein").

15

The nucleotide sequence of AX56\_28 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX56\_28 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14.

20

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX56\_28 should be approximately 4500 bp.

25

The nucleotide sequence disclosed herein for AX56\_28 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX56\_28 demonstrated at least some homology with sequences identified as M20816 (Chicken cytотactин mRNA, partial cds, clone pEC803 [Gallus gallus]), N67571 (yz42a06.s1 Homo sapiens cDNA clone 285682 3'), and T19080 (e05023t Testis 1 Homo sapiens cDNA clone e05023 5' end). The predicted amino acid sequence disclosed herein for AX56\_28 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AX56\_28 protein demonstrated at least some identity with sequences identified as L12018 (putative protein [Caenorhabditis elegans]). Based upon homology, AX56\_28 proteins and each homologous protein or peptide may share at least some activity. The

30

TopPredII computer program predicts a potential transmembrane domain within the AX56\_28 protein sequence (SEQ ID NO:14).

Clone "AX92\_3"

5 A polynucleotide of the present invention has been identified as clone "AX92\_3". AX92\_3 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX92\_3 is a full-length 10 clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX92\_3 protein").

15 The nucleotide sequence of AX92\_3 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX92\_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Amino acids 13 to 25 are a predicted 20 leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 26, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX92\_3 should be approximately 1800 bp.

25 The nucleotide sequence disclosed herein for AX92\_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX92\_3 demonstrated at least some homology with sequences identified as AA003356 (mg49g01.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 427152 5'), AA036247 (mi74a03.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 472300 5'), F19608 (H.sapiens mitochondrial EST sequence (009-X4-35) from skeletal muscle), M10546 (Human mitochondrial DNA, fragment M1, encoding transfer RNAs, cytochrome oxidase I, and 2 URFs [Mitochondrion Homo sapiens]), and U46493 (Cloning vector pFlp recombinase gene, complete cds). Based upon homology, AX92\_3 proteins and each homologous protein or peptide may 30 share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AX92\_3 protein sequence, centered around amino

acids 20, 183, 269, and 295 of SEQ ID NO:16.

Clone "BF245\_1"

5 A polynucleotide of the present invention has been identified as clone "BF245\_1". BF245\_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BF245\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BF245\_1 protein").

10

15 The nucleotide sequence of the 5' portion of BF245\_1 as presently determined is reported in SEQ ID NO:17. An additional internal nucleotide sequence from BF245\_1 as presently determined is reported in SEQ ID NO:18. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:19. Amino acids 18 to 30 of SEQ ID NO:19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 31, or are a transmembrane domain. Additional nucleotide sequence from the 3' portion of BF245\_1, including the polyA tail, is reported in SEQ ID NO:20.

20

25 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BF245\_1 should be approximately 2300 bp.

30 The nucleotide sequence disclosed herein for BF245\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BF245\_1 demonstrated at least some homology with sequences identified as AA001743 (zh86h02.s1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 428211 3' similar to SW YY02\_HUMAN P42285 HYPOTHETICAL MYELOID CELL LINE PROTEIN 2), D29641 (Human mRNA for KIAA0052 gene, partial cds), Q92779 (Human thymopoietin continuous gene fragment), and R39256 (yc91h04.s1 Homo sapiens cDNA clone 23509 3'). The predicted amino acid sequence disclosed herein for BF245\_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BF245\_1 protein

demonstrated at least some identity with sequences identified as Z70271 (W08D2.7 [Caenorhabditis elegans]). Based upon homology, BF245\_1 proteins and each homologous protein or peptide may share at least some activity.

5

Clone "BG33\_7"

10

A polynucleotide of the present invention has been identified as clone "BG33\_7". BG33\_7 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BG33\_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG33\_7 protein").

15

The nucleotide sequence of BG33\_7 as presently determined is reported in SEQ ID NO:21. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BG33\_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BG33\_7 should be approximately 900 bp.

20

The nucleotide sequence disclosed herein for BG33\_7 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BG33\_7 demonstrated at least some homology with sequences identified as AA033818 (zf02c08.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 375758 3') and AA462657 (vg68e04.r1 Soares mouse NbMH Mus musculus cDNA clone 871134 5'). Based upon homology, BG33\_7 proteins and each homologous protein or peptide may share at least some activity.

25

Fig. 2 is an autoradiograph evidencing expression in COS cells of clone BG33\_7 of the present invention.

30

Clone "BM46\_10"

A polynucleotide of the present invention has been identified as clone "BM46\_10". BM46\_10 was isolated from a human adult muscle cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BM46\_10 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BM46\_10 protein").

The nucleotide sequence of BM46\_10 as presently determined is reported in SEQ ID NO:23. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BM46\_10 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:24.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BM46\_10 should be approximately 3600 bp.

The nucleotide sequence disclosed herein for BM46\_10 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BM46\_10 demonstrated at least some homology with sequences identified as F19321 (H.sapiens EST sequence 008-X (391 nt)), N79027 (zb43c09.s1 Homo sapiens cDNA clone 306352 3'), U46493 (Cloning vector pFlp recombinase gene, complete cds), and W74198 (zd74d05.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 346377 3'). Based upon homology, BM46\_10 proteins and each homologous protein or peptide may share at least some activity.

#### Clone "J317\_1"

A polynucleotide of the present invention has been identified as clone "J317\_1". J317\_1 was isolated from a human peripheral blood mononuclear cells (treated with phytohemagglutinin and phorbol myristate acetate and mixed lymphocyte reaction) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. J317\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J317\_1 protein").

The nucleotide sequence of J317\_1 as presently determined is reported in SEQ ID NO:25. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the J317\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:26. Amino acids 19 to 31 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 32, or are a transmembrane domain.

5 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone J317\_1 should be approximately 1300 bp.

10 The nucleotide sequence disclosed herein for J317\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. J317\_1 demonstrated at least some homology with sequences identified as N21491 (yx58f09.s1 Homo sapiens cDNA clone 265961 3'), R39024 (yd08h03.s1 Homo sapiens cDNA clone 25214 3'), T93953 (ye06h06.r1 Homo sapiens cDNA clone 116987 5' similar to contains HGR repetitive element), and Z25379 (H. sapiens partial cDNA sequence; clone C6F07; version 1; strand(+), single read). Based upon homology, J317\_1 proteins and each homologous protein or peptide may share at least some activity.

15

Clone "O289\_1"

20 A polynucleotide of the present invention has been identified as clone "O289\_1". O289\_1 was isolated from a human adult blood (dendritic cells) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. O289\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "O289\_1 protein").

25 The nucleotide sequence of O289\_1 as presently determined is reported in SEQ ID NO:27. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the O289\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:28.

30 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone O289\_1 should be approximately 700 bp.

The nucleotide sequence disclosed herein for O289\_1 was searched against the

GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. O289\_1 demonstrated at least some homology with sequences identified as H59298 (yr04c07.r1 Homo sapiens cDNA clone 204300 5' similar to contains MER22 repetitive element). Based upon homology, O289\_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a large potential transmembrane domain within the O289\_1 protein sequence, centered around amino acid 35 of SEQ ID NO:28. The nucleotide/amino acid sequence of O289\_1 indicates that it may contain MER transposon repetitive elements.

10

Deposit of Clones

15

Clones AC41\_1, AC222\_1, AJ143\_1, AJ168\_4, AK684\_1, AS209\_1, AX92\_3, BF245\_1, BG33\_7, J317\_1 and O289\_1, along with AX56\_8 and BM46\_3 (additional isolates of clones AX56\_28 and BM46\_10, respectively), were deposited on July 9, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98101, from which each clone comprising a particular polynucleotide is obtainable. AX56\_28 was deposited on September 26, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98180; BM46\_10 was deposited on August 23, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98152. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

20

25

30

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1A or Fig. 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from

5 pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the *Clal* site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

10 Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

15 An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

	<u>Clone</u>	<u>Probe Sequence</u>
20	AC41_1	SEQ ID NO:29
	AC222_1	SEQ ID NO:30
	AJ143_1	SEQ ID NO:31
	AJ168_4	SEQ ID NO:32
	AK684_1	SEQ ID NO:33
	AS209_1	SEQ ID NO:34
25	AX56_28	SEQ ID NO:35
	AX92_3	SEQ ID NO:36
	BF245_1	SEQ ID NO:37
	BG33_7	SEQ ID NO:38
	BM46_10	SEQ ID NO:39
30	J317_1	SEQ ID NO:40
	O289_1	SEQ ID NO:41

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as, for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).

5

The design of the oligonucleotide probe should preferably follow these parameters:

10

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- (b) It should be designed to have a  $T_m$  of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

15

The oligonucleotide should preferably be labeled with  $\text{g}^{-32}\text{P}$  ATP (specific activity 6000 Ci/mole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

20

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu\text{l}$  of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100  $\mu\text{g}/\text{ml}$ . The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100  $\mu\text{g}/\text{ml}$  and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

25

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

30

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0

with NaOH) containing 0.5% SDS, 100  $\mu$ g/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then 5 preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 10 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of 15 exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, *Bio/Technology* 10, 773-778 (1992) and in R.S. McDowell, *et al.*, *J. Amer. Chem. Soc.* 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules 20 such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion 25 would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length 30 polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be

determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which the cDNA sequences are derived and any contiguous regions of the genome necessary for the regulated expression of such genes, including but not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

5 The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides .

10 The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

15 The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) <sup>t</sup>	Hybridization Temperature and Buffer <sup>t</sup>	Wash Temperature and Buffer <sup>t</sup>
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	< 50	T <sub>B</sub> *; 1xSSC	T <sub>B</sub> *; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	< 50	T <sub>D</sub> *; 1xSSC	T <sub>D</sub> *; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	< 50	T <sub>F</sub> *; 1xSSC	T <sub>F</sub> *; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	< 50	T <sub>H</sub> *; 4xSSC	T <sub>H</sub> *; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	< 50	T <sub>J</sub> *; 4xSSC	T <sub>J</sub> *; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	< 50	T <sub>L</sub> *; 2xSSC	T <sub>L</sub> *; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	< 50	T <sub>N</sub> *; 6xSSC	T <sub>N</sub> *; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	< 50	T <sub>P</sub> *; 6xSSC	T <sub>P</sub> *; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	< 50	T <sub>R</sub> *; 4xSSC	T <sub>R</sub> *; 4xSSC

<sup>t</sup>: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

<sup>t</sup>: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

\*T<sub>B</sub> - T<sub>R</sub>: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T<sub>m</sub>) of the hybrid, where T<sub>m</sub> is determined according to the following equations. For hybrids less than 18 base pairs in length, T<sub>m</sub>(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T<sub>m</sub>(°C) = 81.5 + 16.6(log<sub>10</sub>[Na<sup>+</sup>]) + 0.41(%G + C) - (600/N), where N is the number of bases in the hybrid, and [Na<sup>+</sup>] is the concentration of sodium ions in the hybridization buffer ([Na<sup>+</sup>] for 1xSSC = 0.165 M).